Supporting Information

Total syntheses of Kavaratamide A and 5-epi-Kavaratamide A

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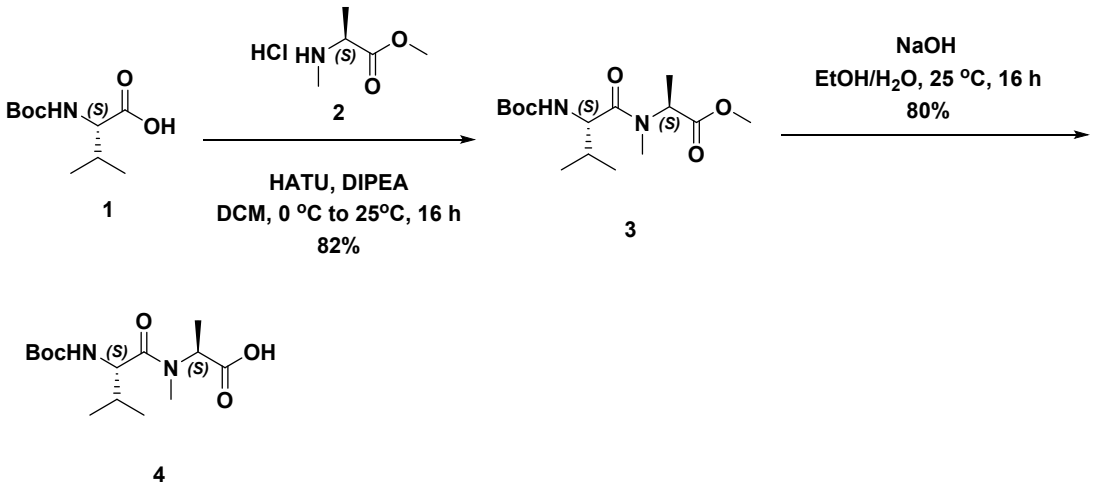
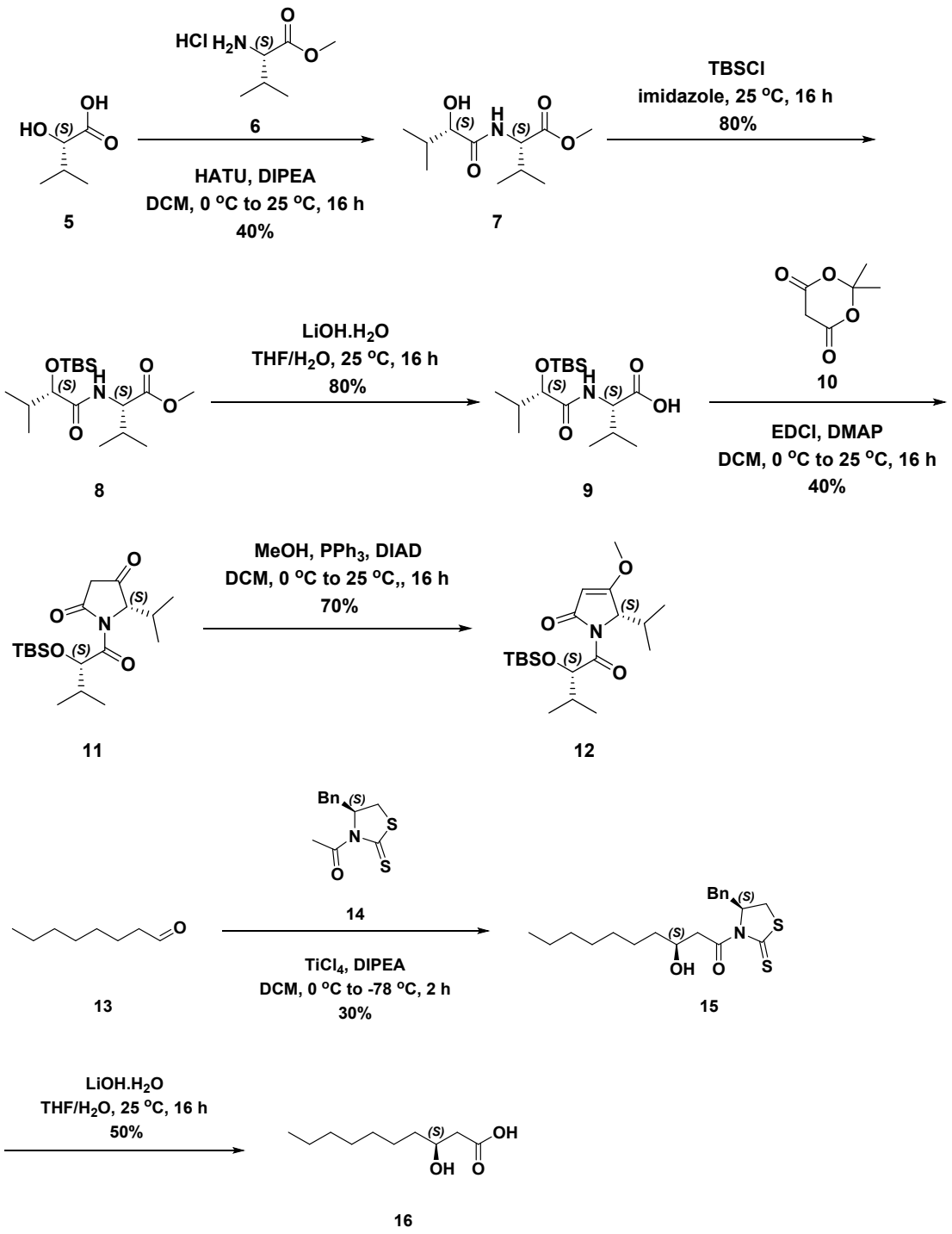
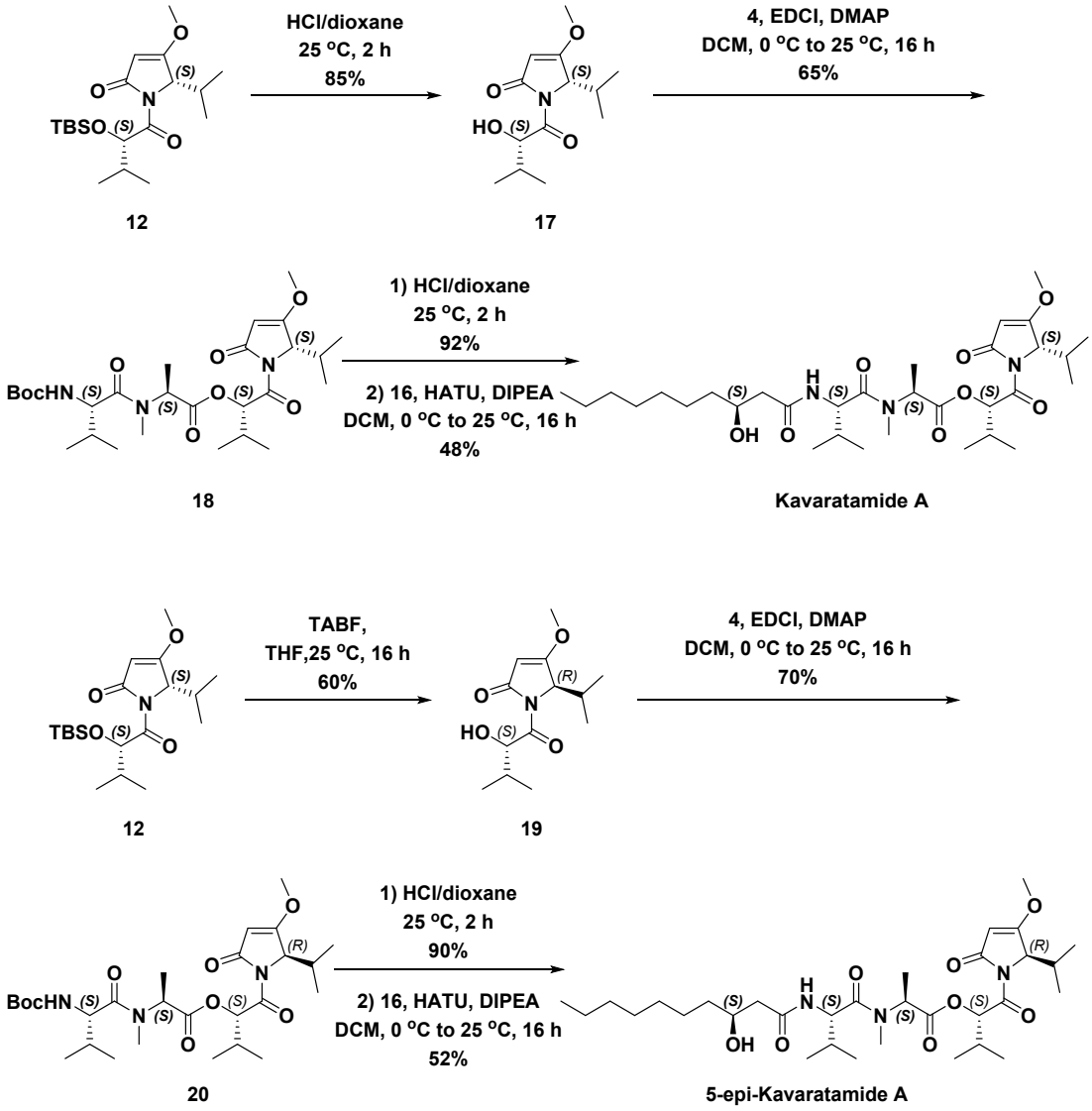
1. General information

All reagents were purchased from commercial suppliers and could be used without purification. All solvents were obtained from commercial sources and purified according to standard procedures. For thin-layer chromatography, a silica gel plate (GF254) was used. The reaction products were purified by column chromatography using silica gel (200-300 mesh). Mass spectrometry was performed using Electrospray Ionization (ESI). NMR spectra were recorded on Brucker-400 NMR spectrometers with tetramethylsilane as the internal standard in $CDCl_3$ or DMSO-D6) (^1H at 400MHz and ^{13}C at 101MHz). All chemical shifts δ are in ppm. The chemical shift (δ ppm) is related to the resonance of the deuterated solvent as the internal references ($CDCl_3$ δ_H= 7.26 ppm, δ_C = 77.16 ppm, DMSO-D6 δ_H= 2.50 ppm, δ_C = 39.60 ppm).

2. General routing

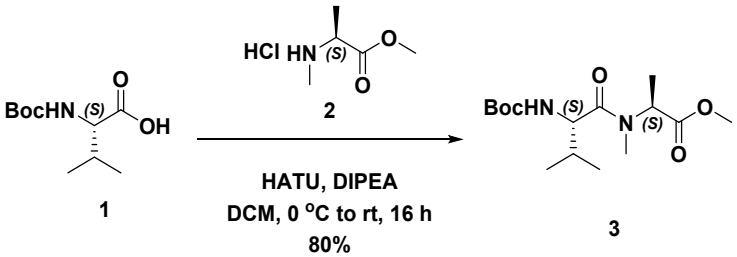



HCl H2N (S) O O
6
HATU, DIPEA
DCM, 0 °C to 25 °C, 16 h
40%
5
7
TBSCl
imidazole, 25 °C, 16 h
80%
LiOH.H2O
THF/H2O, 25 °C, 16 h
80%
8
9
10
EDCI, DMAP
DCM, 0 °C to 25 °C, 16 h
40%
MeOH, PPh3, DIAD
DCM, 0 °C to 25 °C,, 16 h
70%
11
12
14
TiCl4, DIPEA
DCM, 0 °C to -78 °C, 2 h
30%
13
15
LiOH.H2O
THF/H2O, 25 °C, 16 h
50%
16



3. General procedure

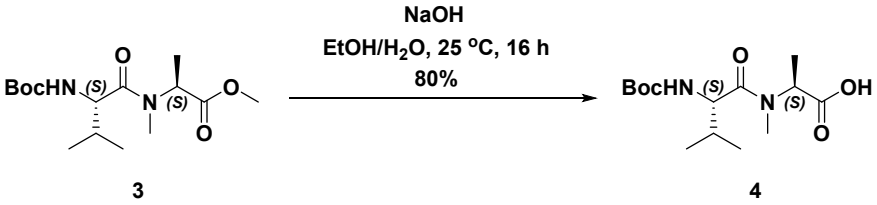
3.1 General procedure for the synthesis of 3



To a solution of compound **1** (1.00 g, 4.60 mmol, 1.0 eq), compound **2** (0.71 g, 4.60 mmol, 1.0 eq) and DIPEA (1.49 g, 11.51 mmol, 2.5 eq) in DCM (10 ml) was added HATU (2.28 g, 5.98 mmol, 1.3 eq) at 0°C under N_2. The resulting solution was stirred

at 25°C under N_2 for 16 hours. Water (20 ml) was added to above solution at 0°C, extracted with EtOAc (30 ml) three times. The organic layers was combined, washed with brine (10 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 5:1) to afford compound **3** (1.20 g, 82.2% yield). [á]25 D= −48.5 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (dt, *J* = 10.3, 4.8 Hz, 2H), 4.47 (p, *J* = 4.3, 3.8 Hz, 1H), 3.70 (d, *J* = 3.5 Hz, 3H), 3.01 (d, *J* = 3.3 Hz, 3H), 2.01 (dt, *J* = 12.3, 6.0 Hz, 1H), 1.42 (t, *J* = 4.7 Hz, 12H), 0.95 (ddd, *J* = 36.7, 7.0, 3.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 171.0, 154.9, 78.5, 76.2, 54.2, 51.2, 51.1, 30.3, 30.3, 27.3, 27.3, 18.4, 16.2, 13.1. HRMS(ES$^+$): m/z Found: 339.1893 [M+Na] $^+$, Calcd.: 339.1890.

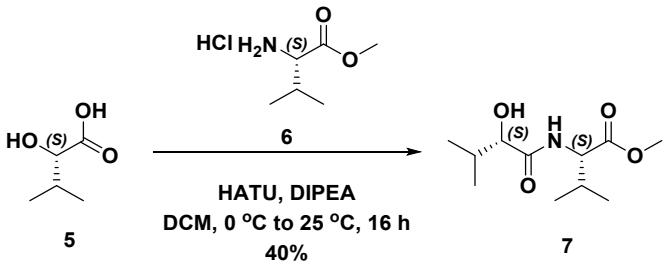
3.2 General procedure for the synthesis of 4



3 4

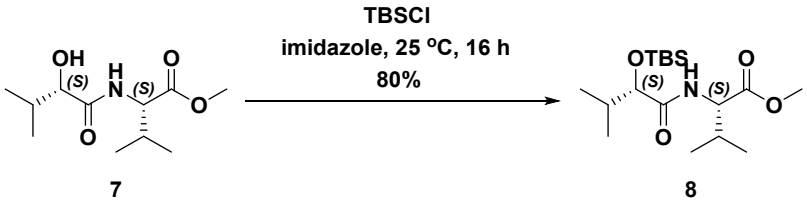
To a solution of compound **3** (400.00 mg, 1.26 mmol, 1.0 eq) in EtOH (3 ml) and H_2O (1 ml) was added NaOH (75.85 mg, 1.90 mmol, 1.5 eq) at 0°C under N_2. The resulting solution was stirred at 25°C under N_2 for 16 hours. The solution was concentrated and NH_4Cl (aq) (10 ml) was added to above mixture, and the resulting mixture was extracted with EtOAc (50 ml) three times. The organic layer was combined, washed with brine (20 ml), dried over Na_2SO_4, filtrated and concentrated to afford crude product, purified by silica gel column (DCM: MeOH = 10:1) to afford compound **4** (306.00 mg, 80.0% yield). [á]25 D= −63.8 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (d, *J* = 9.4 Hz, 1H), 5.25 (d, *J* = 7.4 Hz, 1H), 4.48 (t, *J* = 8.2 Hz, 1H), 3.05 (s, 3H), 1.99 (dp, *J* = 14.7, 7.3 Hz, 1H), 1.43 (d, *J* = 5.4 Hz, 12H), 1.04 – 0.96 (m, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 173.3, 156.0, 79.6, 77.2, 55.3, 52.3, 31.6, 31.2, 28.3, 28.3, 19.3, 17.3, 14.0. HRMS(ES$^+$): m/z Found: 325.1736 [M+Na] $^+$, Calcd.: 325.1734.

3.3 General procedure for the synthesis of 7



To a solution of compound **5** (2.00 g, 16.94 mmol, 1.0 eq), compound **6** (2.12 g, 18.62 mmol, 1.1 eq) and DIPEA (5.48 g, 42.32 mmol, 2.5 eq) in DCM (20 ml) was added HATU (8.36 g, 22.00 mmol, 1.3 eq) at 0°C under N_2. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (40 ml) was added to above solution at 0°C, extracted with EtOAc (60 ml) three times. The organic layers was combined, washed with brine (10 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 3:1) to afford compound **7** (1.60 g, 40.8% yield). [á]25 D= −36.3 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.9 Hz, 1H), 4.42 (dt, *J* = 8.8, 4.3 Hz, 1H), 4.19 (dd, *J* = 13.1, 7.2 Hz, 1H), 3.90 (d, *J* = 5.0 Hz, 1H), 3.64 (d, *J* = 3.8 Hz, 3H), 2.70 (d, *J* = 3.4 Hz, 1H), 2.08 (dt, *J* = 12.9, 6.6 Hz, 2H), 0.95 – 0.71 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 172.4, 76.1, 56.7, 52.0, 31.6, 31.0, 19.0, 19.0, 17.7, 15.6. HRMS(ES$^+$): m/z Found: 254.1365 [M+Na] $^+$, Calcd.: 254.1363.

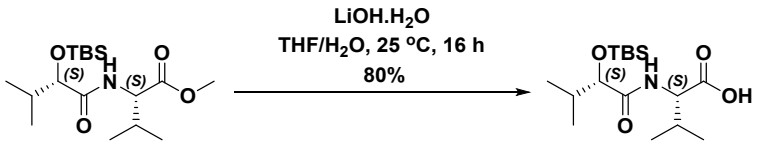
3.4 General procedure for the synthesis of 8



To a solution of compound **7** (1.20 g, 5.19 mmol, 1.0 eq) and imidazole (0.53 g, 7.78 mmol, 1.5 eq) in DCM (15 ml) was added TBSCl (1.17 g, 7.78 mmol, 1.5 eq) at 25°C under N_2. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (20 ml) was added to above solution at 0°C, extracted with EtOAc (30 ml) three times. The organic layers were combined, washed with brine (10 ml), dried over Na_2SO_4, filtrated

and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 5:1) to afford compound **8** (1.43 g, 80.0% yield). [á]25 D= −32.8 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 9.2 Hz, 1H), 4.51 (dt, *J* = 8.8, 3.8 Hz, 1H), 3.95 (d, *J* = 3.4 Hz, 1H), 3.68 (d, *J* = 3.0 Hz, 3H), 2.25 – 2.03 (m, 2H), 0.94 (d, *J* = 3.1 Hz, 9H), 0.94 – 0.82 (m, 12H), 0.06 (d, *J* = 3.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 171.9, 77.7, 56.5, 51.9, 32.7, 31.2, 25.7, 19.3, 19.0, 18.0, 17.7, 16.2, -5.0, -5.3. HRMS(ES^+): m/z Found: 368.2229 $[M+Na]^+$, Calcd.: 368.2228.

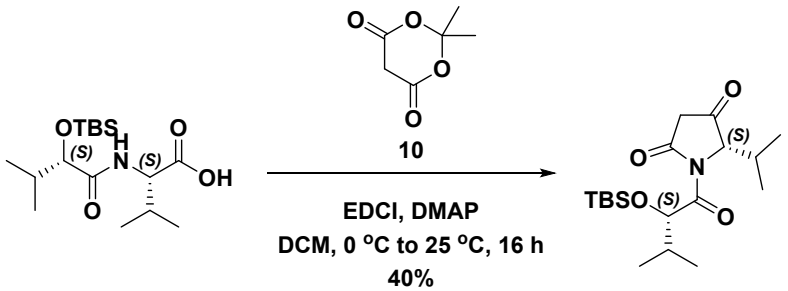
3.5 General procedure for the synthesis of 9



8 **9**

To a solution of compound **8** (1.40 g, 4.05 mmol, 1.0 eq) in THF (15 ml) and H_2O (3 ml) was added LiOH.H_2O (0.25 g, 6.08 mmol, 1.5 eq) at 25°C under N_2. The resulting solution was stirred at 25°C under N_2 for 16 hours. The solution was concentrated to afford crude product, NH_4Cl (aq) (10 ml) was added to above mixture, extracted with EtOAc (20 ml) three times. The organic layers was combined, washed with brine (10 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (DCM : MeOH = 10:1) to afford compound **9** (1.24 g, 72.0% yield). [á]25 D= −48.3 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.13 (d, *J* = 9.1 Hz, 1H), 4.59 (dd, *J* = 9.1, 4.2 Hz, 1H), 4.04 (d, *J* = 3.1 Hz, 1H), 2.26 (td, *J* = 6.9, 4.2 Hz, 1H), 2.12 (s, 1H), 0.96 (d, *J* = 6.3 Hz, 18H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.07 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 174.0, 77.4, 56.4, 32.6, 31.1, 25.8, 19.4, 19.1, 18.0, 17.5, 16.1, -5.0, -5.2. HRMS(ES^+): m/z Found: 354.2070 $[M+Na]^+$, Calcd.: 354.2071.

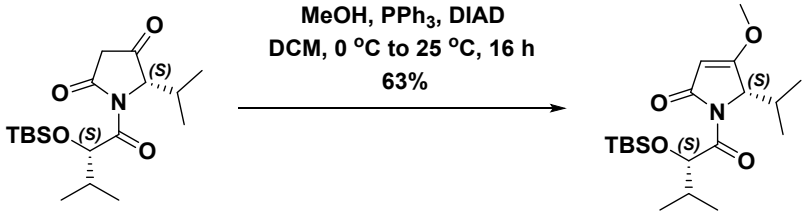
3.6 General procedure for the synthesis of 11



9 11

To a solution of compound **9** (500.00 mg, 1.51 mmol, 1.0 eq) and compound **10** (239.10 mg, 1.66 mmol, 1.1 eq) in DCM (10 ml) was added EDCI (346.94 mg, 1.81 mmol, 1.2 eq) at 0°C under N_2. The resulting solution was stirred at 0°C under N_2 for 2 hours. Then a solution of DMAP (202.68 mg, 1.66 mmol, 1.1 eq) in DCM (2 ml) was added dropwise above solution at 0°C under N_2. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (20 ml) was added to above solution at 0°C, extracted with EtOAc (30 ml) three times. The organic layers was combined, washed with brine (10 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (DCM : MeOH = 10:1) to afford compound **11** (214.50 mg, 40.0 % yield). [á]25 D= −38.5 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 – 5.21 (m, 1H), 4.65 – 4.42 (m, 1H), 3.19 (d, *J* = 5.2 Hz, 2H), 2.75 – 2.50 (m, 1H), 2.10 – 1.92 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 18H), 0.04 (d, *J* = 11.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 202.9, 174.7, 174.4, 169.5, 168.9, 77.3, 76.9, 71.8, 71.1, 44.8, 44.7, 32.4, 31.6, 30.0, 29.6, 25.9, 25.8, 25.8, 25.7, 20.3, 19.9, 18.3, 18.3, 16.0, 15.9, 15.4, 15.0, -4.8, -5.3. HRMS(ES$^+$): m/z Found: 378.2070 [M+Na] $^+$, Calcd.: 378.2071.

3.7 General procedure for the synthesis of 12

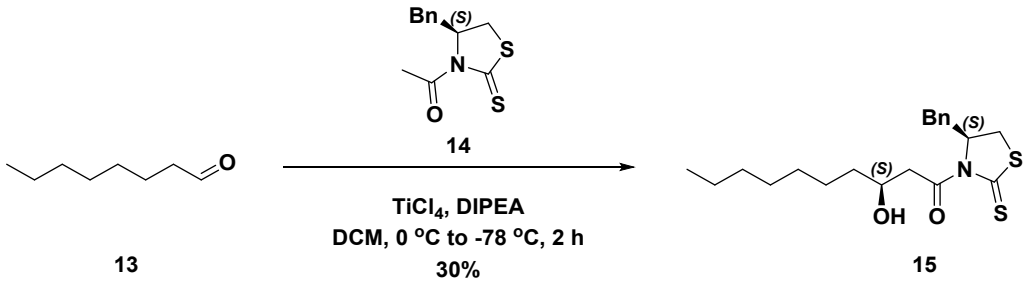


11 12

To a solution of compound **11** (200.00 mg, 0.56 mmol, 1.0 eq), PPh_3 (191.80 mg, 0.73

mmol, 1.3 eq) and MeOH (23.43 mg, 0.73 mmol, 1.3 eq) in DCM (2 ml) was added dropwise a solution of DIAD (147.87 mg, 0.73 mmol, 1.3 eq) in DCM (1 ml) at 0°C under N_2 for 1 hour. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (3 ml) was added to above solution at 0°C, extracted with EtOAc (10 ml) three times. The organic layers were combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 5:1) to afford compound **12** (131.00 mg, 63.0% yield). [á]25 D= −45.2 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (dt, *J* = 6.0, 3.3 Hz, 1H), 5.04 (t, *J* = 3.7 Hz, 1H), 4.50 (d, *J* = 3.9 Hz, 1H), 3.83 (d, *J* = 4.4 Hz, 3H), 2.68 (q, *J* = 7.3 Hz, 1H), 1.97 (dtt, *J* = 12.8, 9.2, 4.8 Hz, 1H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.1 Hz, 3H), 0.92 (q, *J* = 2.8 Hz, 9H), 0.87 (d, *J* = 6.1 Hz, 3H), 0.77 – 0.66 (m, 3H), 0.11 – -0.04 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 173.4, 170.4, 94.80, 75.8, 64.2, 58.4, 31.8, 28.5, 25.9, 25.8, 19.7, 19.0, 18.3, 15.9, 15.0, -4.8, -5.2. HRMS(ES^+): m/z Found: 392.2227 $[M+Na]^+$, Calcd.: 392.2228.

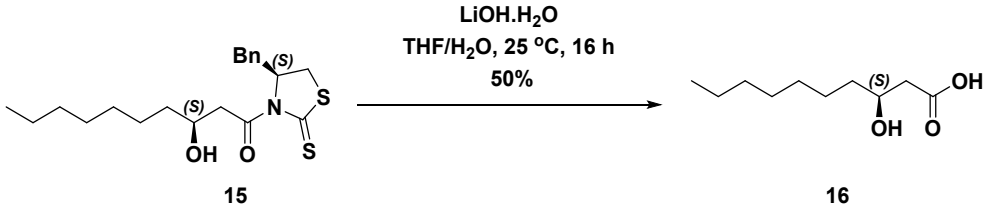
3.8 General procedure for the synthesis of 15



To a solution of compound **14** (100.00 mg, 0.40 mmol, 1.00 eq) in dry DCM (2 ml) was added dropwise $TiCl_4$ (0.44 ml, 0.44 mmol, 1.12 eq, 1M solution in DCM) at 0°C under N_2 for 10 mins. The resulting solution was stirred at 0°C for 30 mins. DIPEA (61.70 mg, 0.48 mmol, 1.20 eq) was added dropwise to above solution at 0°C under N_2 for 10 mins. The resulting solution was stirred at 0°C for 30 mins. Cooled the solution to -78°C, a solution of compound **13** (71.41 mg, 0.56 mmol, 1.4 eq) in dry DCM (1 ml) was added dropwise to above solution for 30 mins. The resulting solution was stirred at -78°C under N_2 for 2h. NH_4Cl (aq) (3 ml) was added to above mixture, extracted with

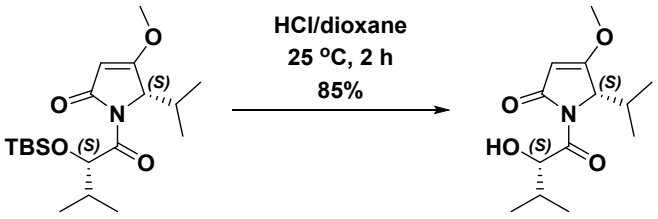
EtOAc (5 ml) three times. The organic layers was combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 3:1) to afford compound **15** (45.50 mg, 30.1% yield). [á]25 D= +78.6 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.27 – 7.20 (m, 3H), 5.36 (ddd, *J* = 10.9, 7.3, 3.8 Hz, 1H), 4.32 – 4.07 (m, 1H), 4.04 – 3.72 (m, 1H), 3.61 (dd, *J* = 17.9, 2.5 Hz, 1H), 3.36 (dt, *J* = 13.9, 6.9 Hz, 1H), 3.19 (dd, *J* = 13.2, 3.9 Hz, 1H), 3.14 – 2.95 (m, 2H), 2.88 (t, *J* = 10.3 Hz, 1H), 1.71 – 1.27 (m, 12H), 0.84 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.4, 174.1, 173.4, 136.4, 129.4, 129.0, 129.0, 127.3, 72.1, 68.3, 67.9, 46.6, 45.9, 44.6, 36.8, 36.4, 32.1, 31.8, 31.8, 29.6, 29.5, 29.2, 25.6, 22.7, 22.7, 14.1. HRMS(ES$^+$): m/z Found: 402.1530 [M+Na] $^+$, Calcd.: 402.1532.

3.9 General procedure for the synthesis of 16



To a solution of compound **15** (40.00 mg, 0.11 mmol, 1.0 eq) in THF (1 ml) and H_2O (0.3 ml) was added LiOH.H_2O (6.63 mg, 0.16 mmol, 1.5 eq) at 25^{o}C under N_2. The resulting solution was stirred at 25^{o}C under N_2 for 16 hours. The solution was concentrated to afford crude product, NH_4Cl (aq) (3 ml) was added to above mixture, extracted with EtOAc (5 ml) three times. The organic layers was combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (DCM : MeOH = 10:1) to afford compound **16** (10.00 mg, 50.4% yield). [á]25 D= +32.5 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (dt, *J* = 8.3, 4.4 Hz, 1H), 2.64 – 2.44 (m, 2H), 1.62 – 1.28 (m, 12H), 0.87 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 68.0, 40.8, 36.5, 31.8, 29.4, 29.2, 25.4, 22.6, 14.1. HRMS(ES$^+$): m/z Found: 187.1337 [M-H] $^-$, Calcd.: 187.1340.

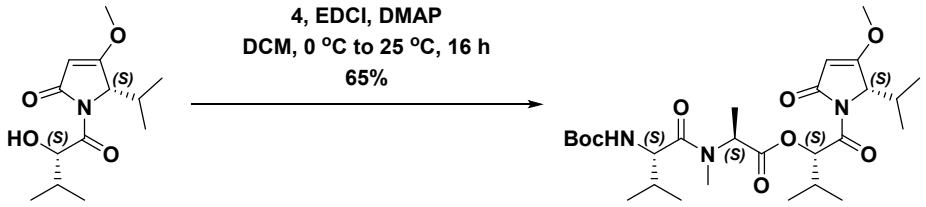
3.10 General procedure for the synthesis of 17



12 17

A solution of compound **12** (150.00 mg, 0.41 mmol, 1 eq) in HCl/ dioxane (4 N) (2 ml) was stirred at 25°C under N_2 for 2 h. The mixture was concentrated to afford a hydrochloride compound **17** (88.00 mg, 84.9% yield). The product would be used to next step without further purification. [á]25 D= −36.4 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (s, 1H), 4.75 (d, *J* = 3.8 Hz, 1H), 4.53 (d, *J* = 2.6 Hz, 1H), 3.86 (s, 3H), 2.73 – 2.63 (m, 1H), 2.20 – 2.07 (m, 1H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H). HRMS(ES$^+$): m/z Found: 278.1373 [M+Na] $^+$, Calcd.: 278.1363.

3.11 General procedure for the synthesis of 18

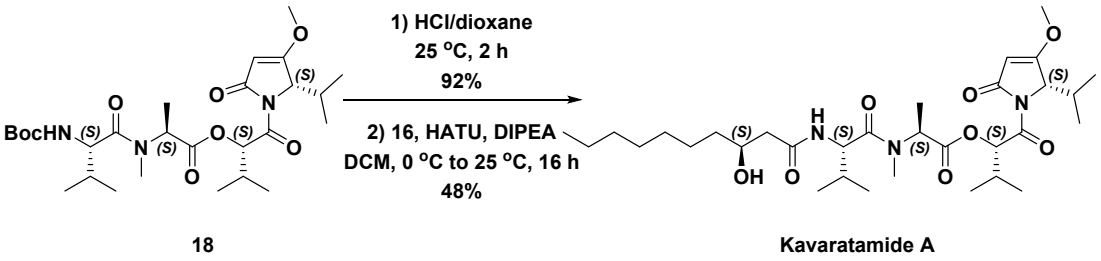


17 18

To a solution of compound **17** (35.00 mg, 0.14 mmol, 1.0 eq) and compound **4** (53.89 mg, 0.18 mmol, 1.3 eq) in DCM (2 ml) was added EDCI (39.42 mg, 0.21 mmol, 1.5 eq) at 0°C under N_2. The resulting solution was stirred at 0°C under N_2 for 30 mins. Then a solution of DMAP (3.35 mg, 0.027 mmol, 0.2 eq) in DCM (1 ml) was added dropwise above solution at 0°C under N2. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (3 ml) was added to above solution at 0°C, extracted with EtOAc (5 ml) three times. The organic layers was combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by

silica gel column (PE : EtOAc = 1:1) to afford compound **18** (48.00 mg, 64.9 % yield). [á]25 D= −22.5 (c = 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (d, *J* = 3.2 Hz, 1H), 5.29 (t, *J* = 7.8 Hz, 2H), 5.06 (s, 1H), 4.48 (dd, *J* = 7.3, 2.7 Hz, 2H), 3.84 (s, 3H), 3.06 (d, *J* = 34.4 Hz, 3H), 2.58 (ddt, *J* = 11.9, 7.5, 4.5 Hz, 1H), 2.21 (pd, *J* = 6.8, 3.1 Hz, 1H), 1.99 (dq, *J* = 12.8, 6.6 Hz, 1H), 1.43 (d, *J* = 10.9 Hz, 12H), 1.08 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.90 (dd, *J* = 11.1, 6.6 Hz, 6H), 0.77 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 172.4, 171.1, 170.0, 169.0, 155.9, 94.6, 79.4, 78.2, 64.2, 58.5, 55.1, 52.5, 31.8, 31.3, 28.7, 28.3, 19.7, 19.5, 18.7, 17.1, 16.0, 15.2, 14.1. HRMS(ES^{+}): m/z Found: 562.3105 [M+H] $^{+}$, Calcd.: 562.3099.

3.12 General procedure for the synthesis of Kavaratamide A

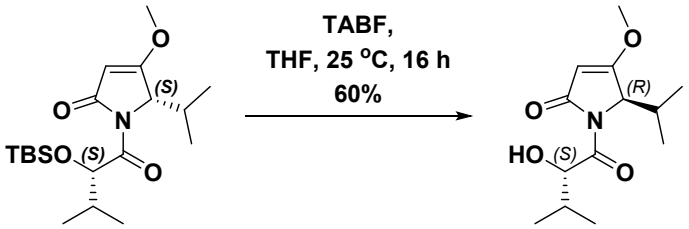


18 **Kavaratamide A**

A solution of compound **18** (15.00 mg, 0.028 mmol, 1.0 eq) in HCl/ dioxane (4 N) (1 ml) was stirred at 25°C under N_2 for 2 h. The mixture was concentrated to afford a hydrochloride compound **18a** (12.20 mg, 92.2% yield). The product would be used to next step without further purification. To a solution of compound **18a** (12.20 mg, 0.026 mmol, 1.0 eq), compound **16** (5.31 mg, 0.028 mmol, 1.1 eq) and DIPEA (8.28 mg, 0.064 mmol, 2.5 eq) in DCM (1 ml) was added HATU (14.62 mg, 0.038 mmol, 1.5 eq) at 0°C under N_2. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (2 ml) was added to above solution at 0°C, extracted with EtOAc (4 ml) three times. The organic layers was combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 1:1) to afford **Kavaratamide A** (7.50 mg, 48.0% yield). [á]25 D= −12.5 (c = 1.0, MeOH). IR (KBr) νmax: 3309, 2962, 2928, 2855, 1731, 1696, 1630, 1456, 1398, 1342, 1319, 1251, 1212, 1125, 1092, 1007, 943, 832, 703, 665 cm^{-1}.^{1}H NMR (400

MHz, $CDCl_3$) δ 6.48 (d, *J* = 8.9 Hz, 1H), 5.82 (d, *J* = 3.2 Hz, 1H), 5.28 (q, *J* = 7.2 Hz, 1H), 5.07 (s, 1H), 4.83 (dd, *J* = 8.9, 5.5 Hz, 1H), 4.50 (d, *J* = 2.7 Hz, 1H), 3.95 (s, 1H), 3.85 (s, 3H), 3.04 (s, 3H), 2.59 (tt, *J* = 7.1, 4.5 Hz, 1H), 2.38 (dd, *J* = 14.9, 2.8 Hz, 1H), 2.30 (d, *J* = 9.1 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.05 (dt, *J* = 12.5, 6.5 Hz, 1H), 1.53 (dd, *J* = 8.8, 7.8 Hz, 1H), 1.45 (d, *J* = 7.3 Hz, 3H), 1.42 – 1.39 (m, 1H), 1.27 (m, 10H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 172.9, 172.2, 171.1, 170.1, 169.1, 94.7, 78.4, 69.0, 64.4, 58.7, 53.9, 52.7, 42.9, 37.1, 31.9, 31.9, 31.3, 29.7, 29.4, 28.9, 28.5, 25.6, 22.9, 19.8, 19.8, 18.8, 17.4, 16.1, 15.3, 14.3, 14.2. HRMS(ES^+): m/z Found: 632.3890 $[M+Na]^+$, Calcd.: 632.3881.

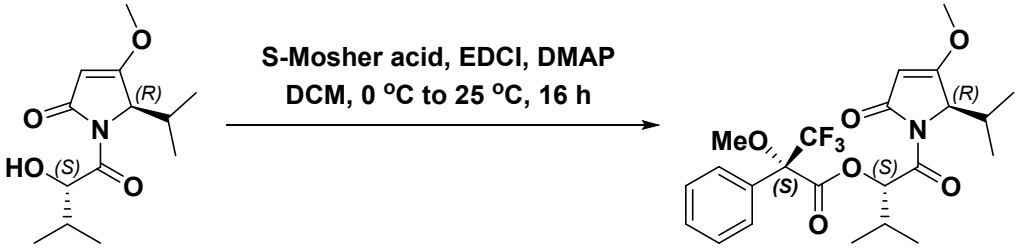
3.13 General procedure for the synthesis of 19



12 **19**

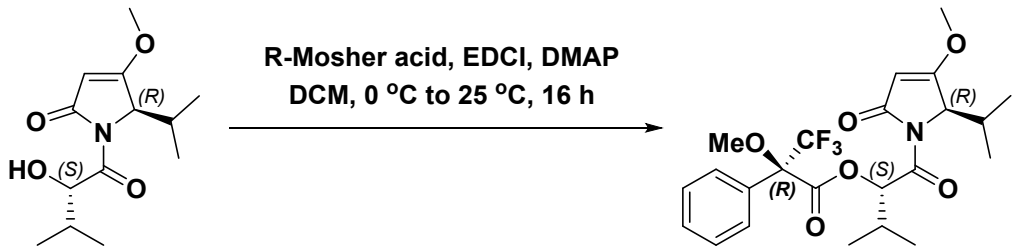
To a solution of compound **12** (130.00 mg, 0.35 mmol, 1.0 eq) in THF (2 ml) was added TBAF (137.96 mg, 0.53 mmol, 1.5 eq) at 25°C under N_2. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (2 ml) was added to above solution at 0°C, extracted with EtOAc (4 ml) three times. The organic layers were combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 1:1) to afford compound **19** (54.00 mg, 60.1% yield). [á]25 D= +12.6 (c = 0.1, MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.99 (s, 1H), 4.64 (d, *J* = 2.7 Hz, 1H), 3.86 (s, 3H), 3.31 (d, *J* = 7.5 Hz, 1H), 2.45 (pd, *J* = 7.1, 2.7 Hz, 1H), 2.18 (pd, *J* = 6.8, 2.6 Hz, 1H), 1.12 (d, *J* = 7.0 Hz, 6H), 0.75 (dd, *J* = 6.9, 4.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 175.1, 169.5, 94.3, 75.8, 63.7, 58.7, 32.2, 28.7, 20.0, 18.6, 15.3, 14.7. HRMS(ES^+): m/z Found: 278.1373 $[M+Na]^+$, Calcd.: 278.1363.

3.14 General procedure for the synthesis of *S*-Mosher ester



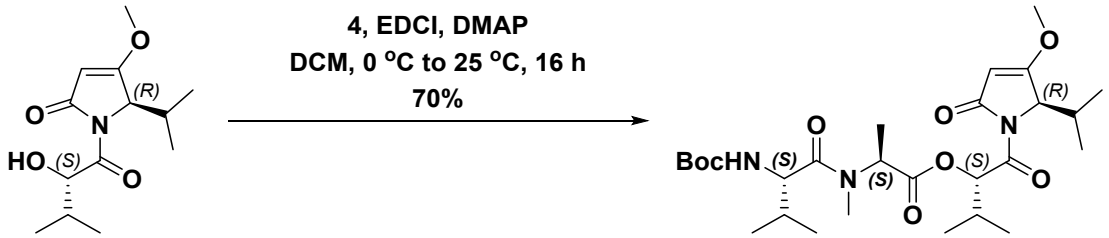
To a solution of compound **19** (5.00 mg, 0.019 mmol, 1.0 eq) and *S*-Mosher acid (5.04 mg, 0.021 mmol, 1.1 eq) in DCM (1 ml) was added EDCI (5.63 mg, 0.029 mmol, 1.5 eq) at 0°C under N_2. The resulting solution was stirred at 0°C under N_2 for 30 mins. Then a solution of DMAP (0.48 mg, 0.004 mmol, 0.2 eq) in DCM (0.5 ml) was added dropwise above solution at 0°C under N2. The resulting solution was stirred at 25°C under N_2 for 6 hours. Water (3 ml) was added to above solution at 0°C, extracted with EtOAc (5 ml) three times. The organic layers was combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 1:1) to afford ***S*-Mosher ester** (6.00 mg, 65.0 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.41 (dd, *J* = 5.3, 2.0 Hz, 3H), 6.07 (d, *J* = 3.0 Hz, 1H), 5.10 (s, 1H), 4.68 (d, *J* = 2.8 Hz, 1H), 3.87 (s, 3H), 3.67 (d, *J* = 1.3 Hz, 3H), 2.50 (qt, *J* = 7.0, 3.5 Hz, 1H), 2.36 (pd, *J* = 6.8, 2.9 Hz, 1H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H).

3.15 General procedure for the synthesis of *R*-Mosher ester



To a solution of compound **19** (5.00 mg, 0.019 mmol, 1.0 eq) and R-Mosher acid (5.04 mg, 0.021 mmol, 1.1 eq) in DCM (1 ml) was added EDCI (5.63 mg, 0.029 mmol, 1.5 eq) at 0°C under N_2. The resulting solution was stirred at 0°C under N_2 for 30 mins. Then a solution of DMAP (0.48 mg, 0.004 mmol, 0.2 eq) in DCM (0.5 ml) was added dropwise above solution at 0°C under N_2. The resulting solution was stirred at 25°C under N_2 for 6 hours. Water (3 ml) was added to above solution at 0°C, extracted with EtOAc (5 ml) three times. The organic layers was combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 1:1) to afford ***R*-Mosher ester** (6.00 mg, 65.0 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.46 – 7.37 (m, 3H), 6.10 (d, *J* = 2.9 Hz, 1H), 5.10 (s, 1H), 4.67 (d, *J* = 2.8 Hz, 1H), 3.86 (s, 3H), 3.57 (d, *J* = 1.1 Hz, 3H), 2.49 (dtd, *J* = 13.8, 6.9, 2.7 Hz, 1H), 2.41 (qt, *J* = 6.9, 3.4 Hz, 1H), 1.13 (dd, *J* = 9.4, 7.0 Hz, 6H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H).

3.16 General procedure for the synthesis of 20

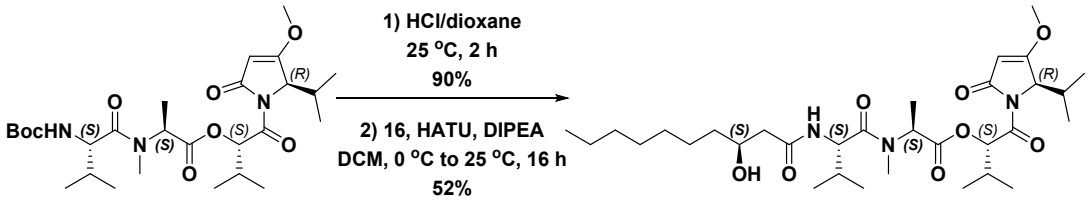


19 **20**

To a solution of compound **19** (35.00 mg, 0.14 mmol, 1.0 eq) and compound **4** (53.89 mg, 0.18 mmol, 1.3 eq) in DCM (2 ml) was added EDCI (39.42 mg, 0.21 mmol, 1.5 eq) at 0°C under N_2. The resulting solution was stirred at 0°C under N_2 for 30 mins. Then a solution of DMAP (3.35 mg, 0.027 mmol, 0.2 eq) in DCM (1 ml) was added dropwise above solution at 0°C under N2. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (3 ml) was added to above solution at 0°C, extracted with EtOAc (5 ml) three times. The organic layers was combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 1:1) to afford compound **20** (52.00 mg, 70.3 % yield). [á]25 D= −30.6 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (q, *J*

= 3.3, 2.8 Hz, 1H), 5.31 (dt, *J* = 15.7, 8.3 Hz, 2H), 5.05 (s, 1H), 4.58 (d, *J* = 2.6 Hz, 1H), 4.46 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.83 (s, 3H), 3.07 (d, *J* = 36.3 Hz, 3H), 2.54 – 2.24 (m, 2H), 1.99 (td, *J* = 13.6, 12.7, 6.2 Hz, 1H), 1.47 (d, *J* = 7.5 Hz, 3H), 1.41 (s, 9H), 1.07 (dd, *J* = 7.1, 4.0 Hz, 6H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 6H), 0.71 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 172.5, 171.3, 169.6, 168.8, 155.9, 94.3, 79.4, 78.5, 63.6, 63.6, 58.6, 55.1, 52.4, 31.7, 31.3, 30.0, 29.7, 28.6, 28.3, 19.7, 19.6, 18.7, 17.0, 15.9, 15.3, 14.2. HRMS(ES^+): m/z Found: 562.3108 $[M+Na]^+$, Calcd.: 562.3099.

3.17 General procedure for the synthesis of 5-epi-Kavaratamide A



20 **5-epi-Kavaratamide A**

A solution of compound **20** (15.00 mg, 0.028 mmol, 1.0 eq) in HCl/ dioxane (4 N) (1 ml) was stirred at 25°C under N_2 for 2 h. The mixture was concentrated to afford a hydrochloride compound **20a** (12.00 mg, 90.7% yield). The product would be used to next step without further purification. To a solution of compound **20a** (12.00 mg, 0.025 mmol, 1.0 eq), compound **16** (5.22 mg, 0.028 mmol, 1.1 eq) and DIPEA (8.15 mg, 0.063 mmol, 2.5 eq) in DCM (1 ml) was added HATU (14.38 mg, 0.038 mmol, 1.5 eq) at 0°C under N_2. The resulting solution was stirred at 25°C under N_2 for 16 hours. Water (2 ml) was added to above solution at 0°C, extracted with EtOAc (4 ml) three times. The organic layers was combined, washed with brine (3 ml), dried over Na_2SO_4, filtrated and concentrated to afford a crude product, purified by silica gel column (PE : EtOAc = 1:1) to afford **5-epi-Kavaratamide A** (8.00 mg, 52.0% yield). [á]25 D= −50.5 (c = 0.1, MeOH).^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, *J* = 8.9 Hz, 1H), 5.95 – 5.83 (m, 1H), 5.33 (q, *J* = 7.5, 7.1 Hz, 2H), 5.07 (s, 1H), 4.89 – 4.79 (m, 1H), 4.60 (s, 1H), 3.95 (s, 1H), 3.85 (s, 3H), 3.06 (s, 3H), 2.47 – 2.29 (m, 3H), 2.28 – 2.17 (m, 1H), 2.08 – 1.97 (m, 2H), 1.50 (d, *J* = 7.4 Hz, 3H), 1.43 (s, 2H), 1.28 (s, 10H), 1.10 (t, *J* = 6.3 Hz, 6H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 9H), 0.73 (d, *J* = 6.9 Hz, 3H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 178.8, 171.7, 171.2, 170.2, 168.6, 167.7, 93.3, 77.5, 67.8, 62.6, 57.6, 52.7, 51.5, 41.8, 35.9, 30.8, 30.7, 29.0, 28.7, 28.5, 28.2, 27.6, 24.4, 21.6, 18.7, 18.6, 17.7, 16.2, 14.9, 14.2, 13.3, 13.1. HRMS(ES^+): m/z Found: 632.3887 $[M+Na]^+$, Calcd.: 632.3881.

4.Cytotoxicity Assays for Kavaratamide A and 5-epi-Kavaratamide A

A viability assay was carried out to evaluate the cytotoxic activity of kavaratamide **A** and 5-epi-kavaratamide **A** in U251, 4T1, HepG2 and PANC1 cells. Cells were seeded at 2 × 10^4 cells/mL into white 96-well plates for overnight and then exposed to kavaratamide **A** and 5-epi-kavaratamide **A** at concentration of 0.01-100 μM. After 72 hours incubation, 10 μl of CCK−8 regent was added to each well and incubated for 2.5 h at 37 ◦C. The absorbance at 450 nm was measured using a microplate reader.

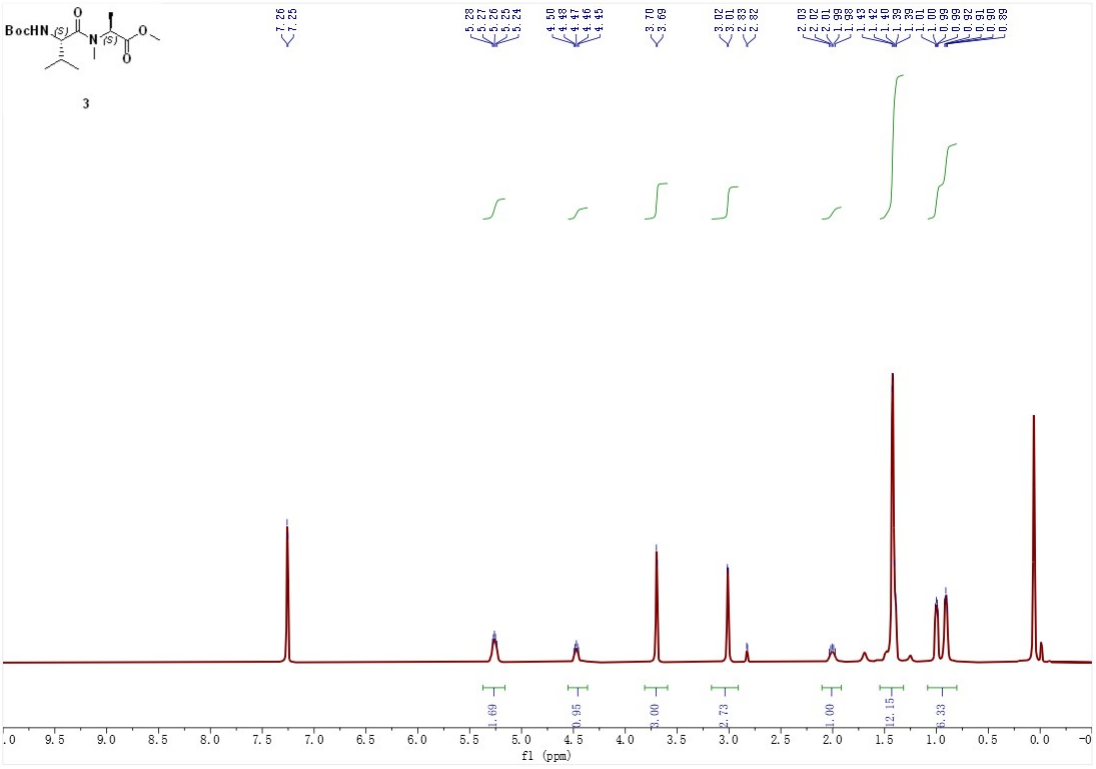
5. Comparison of the Spectra of Isolated and Synthetic Compounds

NMR comparison of natural **Kavaratamide A** [500 MHz (^{1} H) and 125 MHz (^{13}C) in $CDCl_3$] and synthetic **Kavaratamide A** [400 MHz (^{1} H) and 100 MHz (^{13}C) in $CDCl_3$].

Position		Natural **Kavaratamide A**		Synthetic **Kavaratamide A**		Difference value	
		δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H	δ_C
iPr-O-Me-Pyr	1	3.85, s	58.7, CH3	3.85, s	58.7	0.0	0.0
	2		170.2, C		170.1		-0.1
	3	5.07, s	94.7, CH	5.07, s	94.7	0.0	0.0
	4		180.0, C		180.0		0.0
	5	4.50, d (2.5)	64.4, CH	4.50, d (2.7)	64.4	0.0	0.0
	6	2.56, sepd (7.5, 2.5)	28.5, CH	2.59, sepd (7.1, 4.5)	28.5	0.03	0.0
	7	1.09, d (7.5)	18.8, CH3	1.09, d (7.2)	18.8	0.0	0.0
	8	0.78, d (7.0)	15.3, CH3	0.78, d (6.9)	15.3	0.0	0.0
Hiva	9		169.1, C		169.1		0.0
	10	5.82, d (3.5)	78.4, CH	5.82, d (3.2)	78.4	0.0	0.0
	11	2.23, sepd (6.5, 3.0)	28.9, CH	2.23, m	28.9	0.0	0.0
	12	1.05, d (6.5)	19.8, CH3	1.04, d (6.7)	19.8	-0.01	0.0
	13	0.92, d (7.0)	16.1, CH3	0.92, d (6.5)	16.1	0.0	0.0
N-Me-Ala	14		171.1, C		171.1		0.0
	15	5.29, q (7.0)	52.8, CH	5.28, q (7.2)	52.8	-0.01	0.0
	16	1.46, d (7.0)	14.2, CH3	1.45, d (7.3)	14.2	-0.01	0.0
	17	3.04, s	31.9, CH3	3.04, s	31.9	0.0	0.0
Val	18		172.3, C		172.2		-0.1
	19	4.84, dd (8.5, 5.5)	53.9, CH	4.83, dd (8.9, 5.5)	53.9	-0.01	0.0
	20	2.06, sep (7.0)	31.3, CH	2.06, dt (12.5, 6.5)	31.3	-0.01	0.0
	21	1.01, d (7.0)	19.8, CH3	1.01, d (6.8)	19.8	0.0	0.0
	22	0.91, d (6.5)	17.4, CH3	0.90, d (6.3)	17.4	-0.01	0.0
	19-NH	6.54, d (8.5)		6.48, d (8.9)		-0.06	

3-HDA	23		172.9, C		172.9		0.0
	24a	2.38, dd (15.0, 2.5)	42.9, CH2	2.38, dd (14.9, 2.8)	42.9	0.0	0.0
	24b	2.29, dd (15.0, 9.5)		2.30, d (9.1)		0.01	
		3.95, br s					
	25		69.0, CH	3.95, br s	69.0	0.0	0.0
	26a	1.54, dd (17.0, 7.5)	37.1, CH2	1.53, dd (8.3, 7.8)	37.1	-0.01	0.0
		1.42, overlap		1.42, overlap			
	26b					0.0	
	27	1.43–1.24, m	25.6, CH2	1.43–1.24, m	25.6	0.0	0.0
	28	1.43–1.24, m	29.7c , CH2	1.43–1.24, m	29.7	0.0	0.0
	29	1.43–1.24, m	29.4c , CH2	1.43–1.24, m	29.4	0.0	0.0
	30	1.43–1.24, m	31.9, CH2	1.43–1.24, m	31.9	0.0	0.0
	31	1.43–1.24, m	22.8, CH2	1.43–1.24, m	22.8	0.0	0.0
	32	0.88, t (7.0)	14.3, CH3	0.87, t (6.7)	14.3	-0.01	0.0

6.The copies of ^{1}H, ^{13}C NMR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7.25
5.28
5.27
5.26
5.25
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4.50
4.48
4.47
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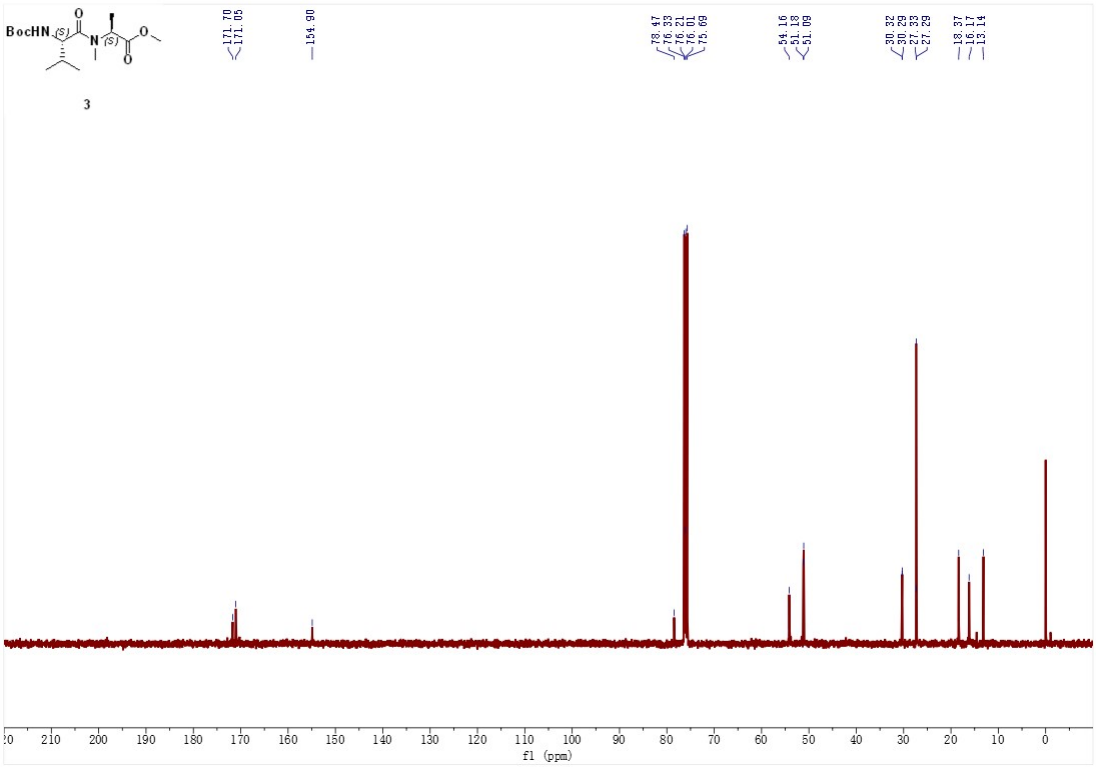
4.45
3.70
3.69
3.02
3.01
2.83
2.82
2.03
2.02
2.01
1.99
1.98
1.53
1.42
1.40
1.39
1.01
1.00
0.99
0.92
0.91
0.90
0.89
1.69
0.95
3.00
2.73
1.00
2.15
3.33
f1 (ppm)


BocHN
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171.05
154.90
78.47
76.33
76.21
76.01
75.69
54.16
51.13
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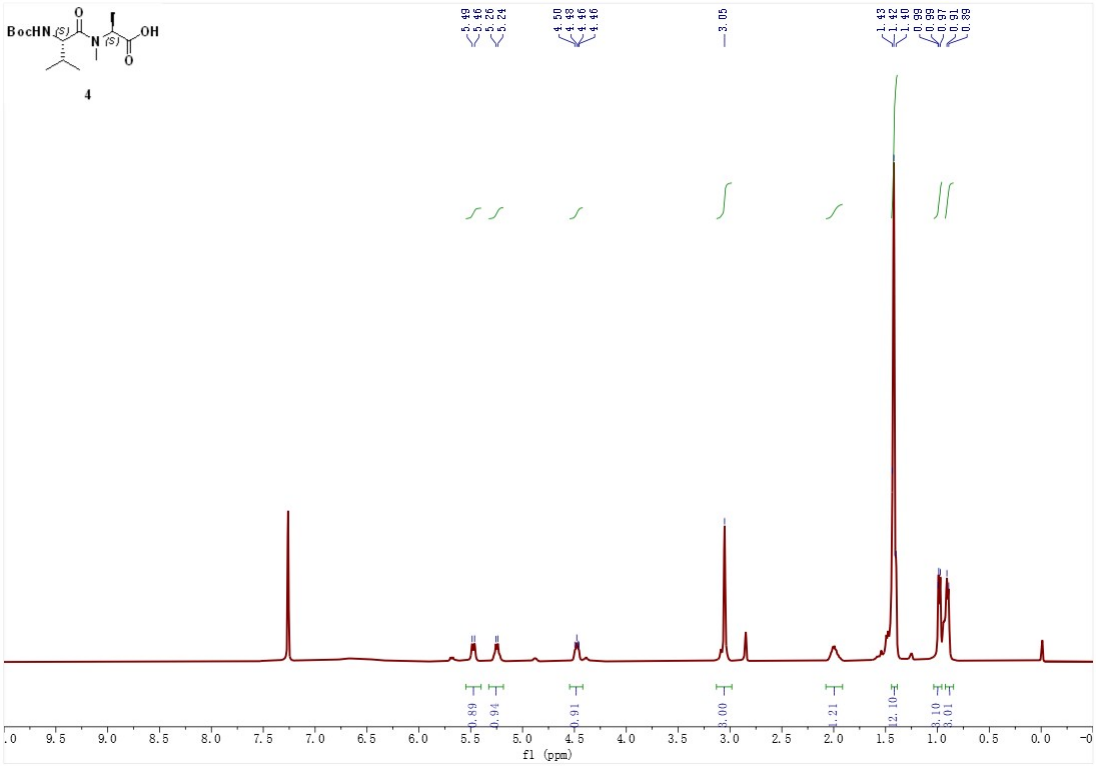
30.29
27.33
27.29
18.37
16.17
13.14
f1 (ppm)


BocHN
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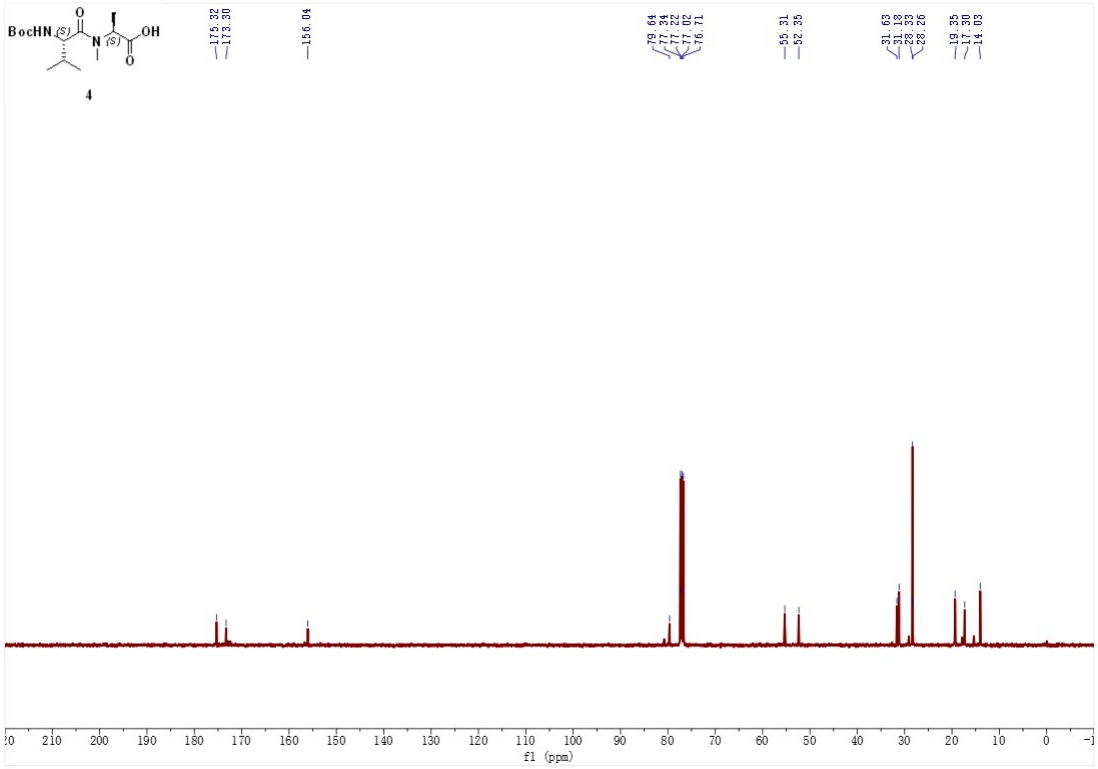
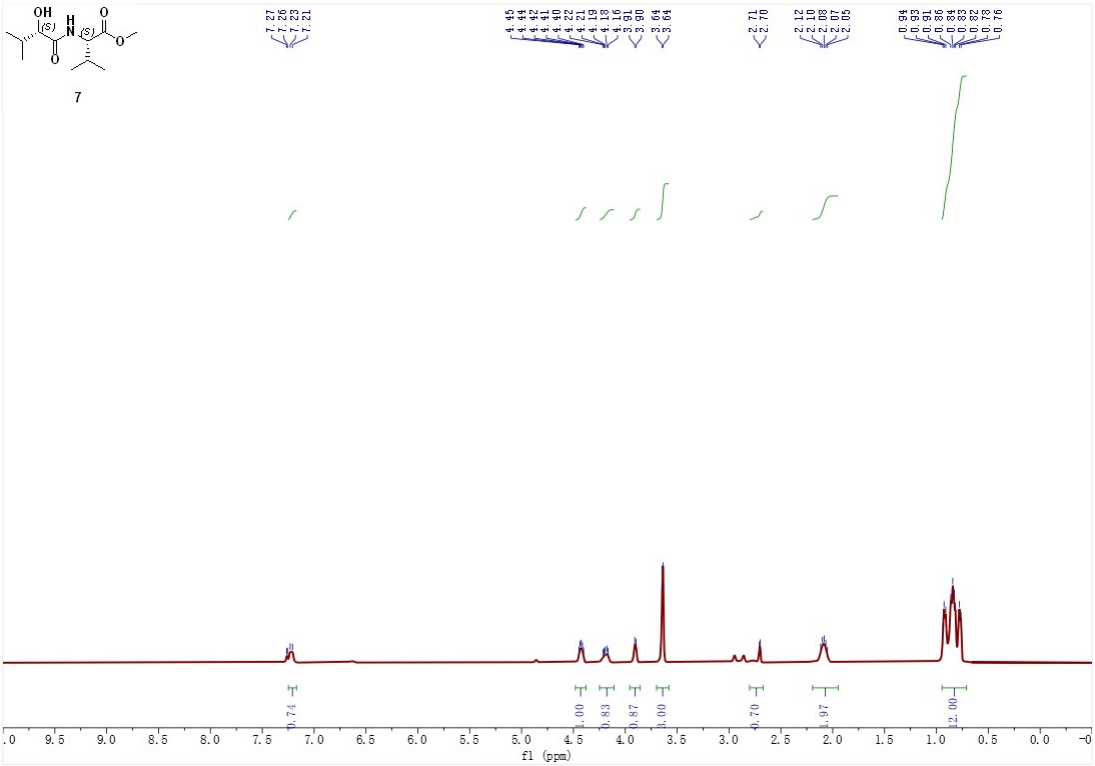
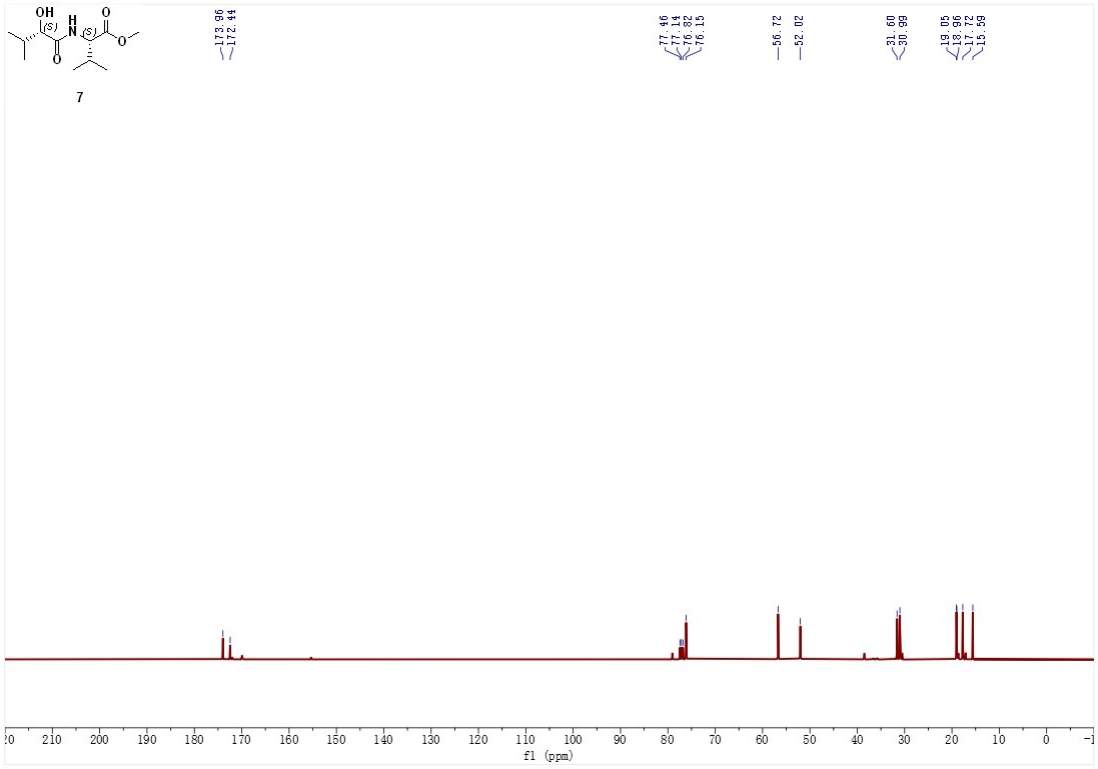
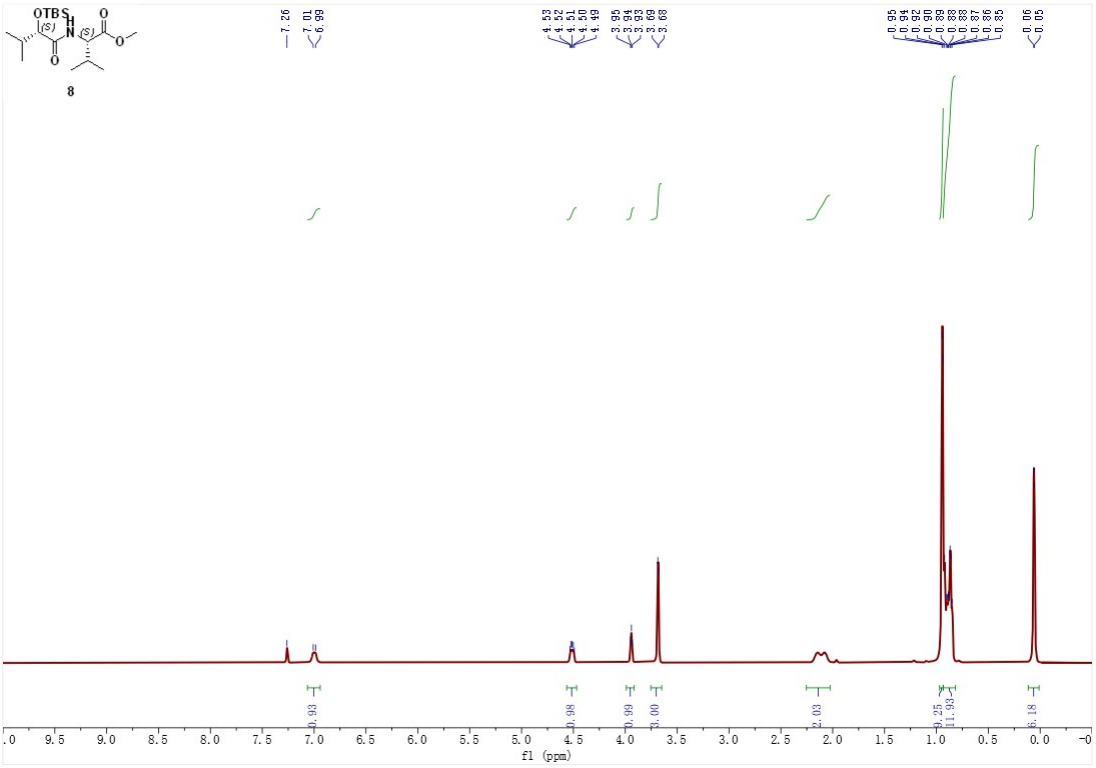
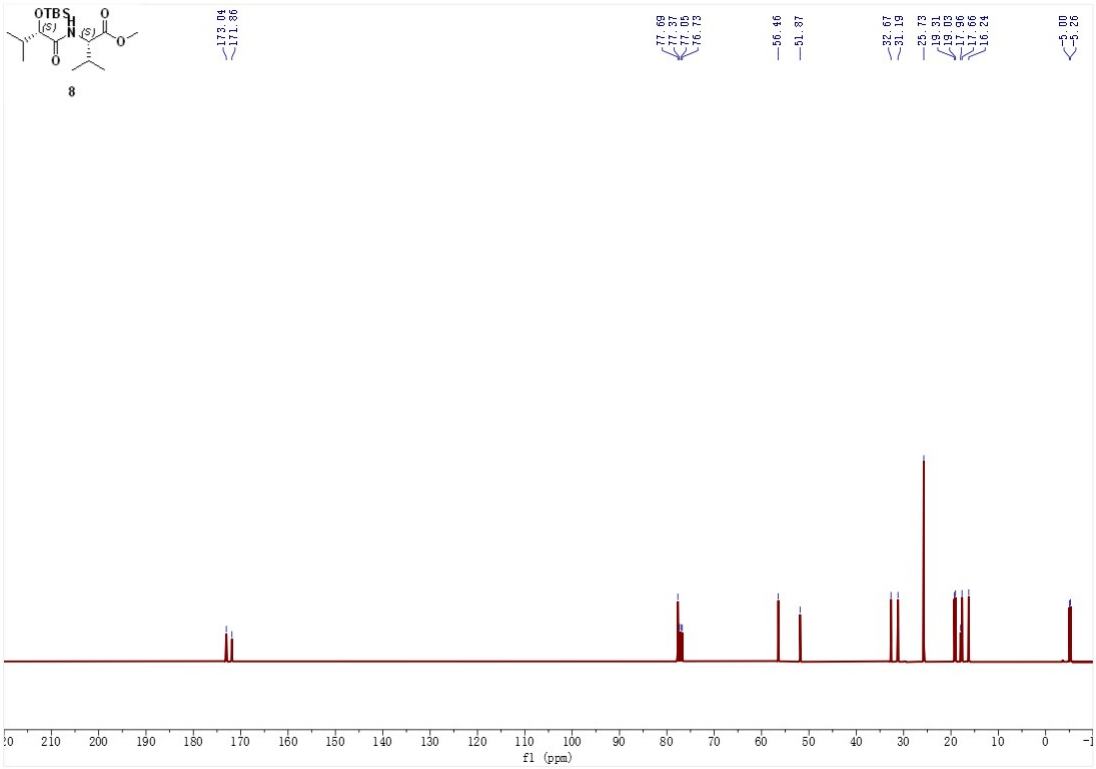
1.42
1.40
0.93
0.93
0.97
0.91
0.89
0.89
0.94
0.91
3.00
4.21
12.10
3.10
3.01
f1 (ppm)

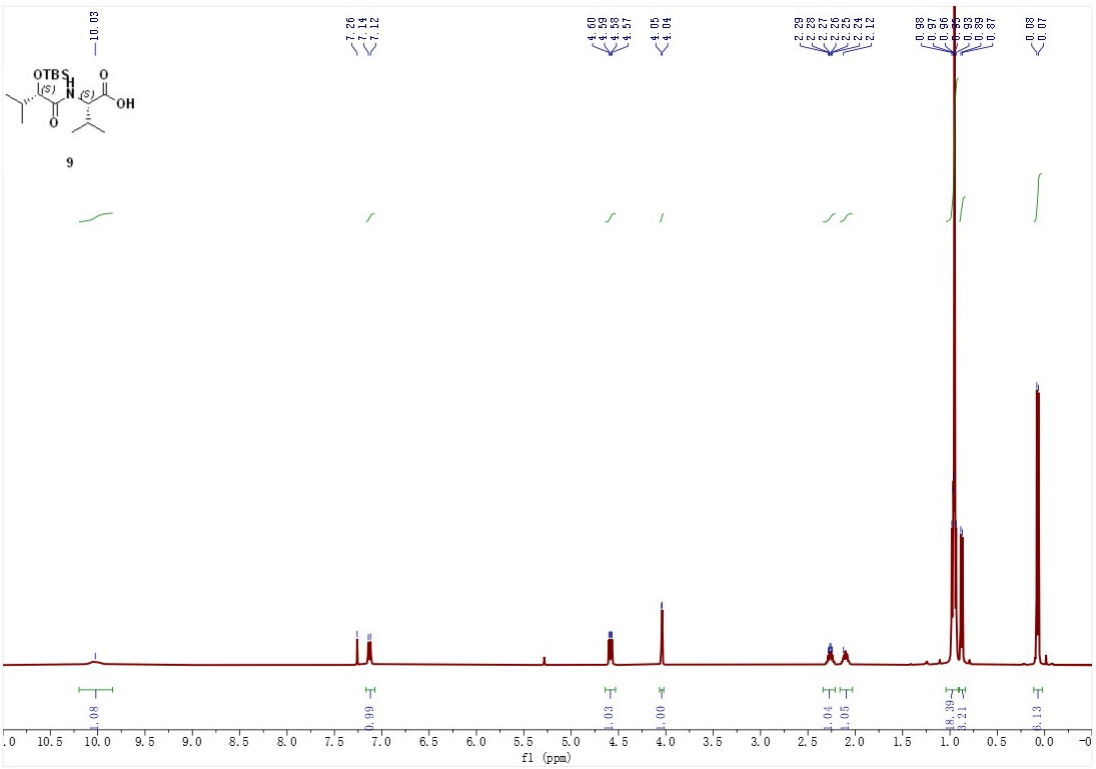

BocHN
OH
4
175.32
173.30
156.04
79.64
77.34
77.22
77.02
76.71
55.31
52.35
31.63
31.18
28.33
28.26
19.35
17.30
14.03
f1 (ppm)

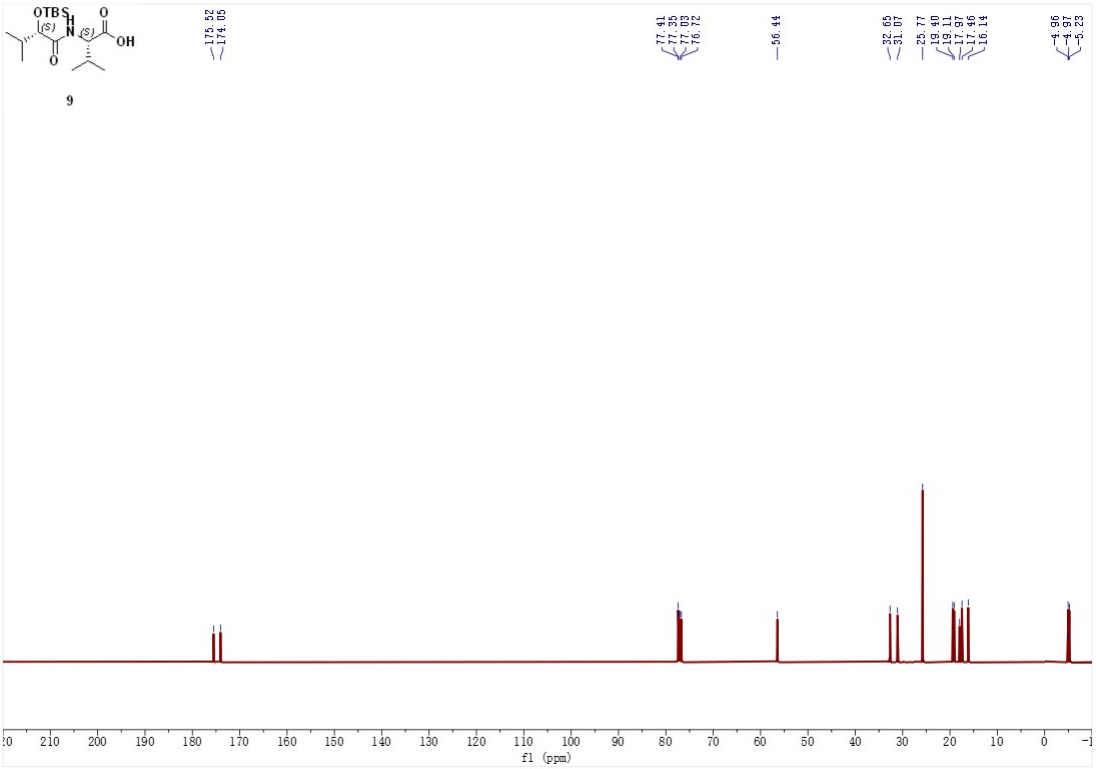

7
7.27
7.26
7.23
7.21
4.45
4.44
4.42
4.41
4.40
4.22
4.21
4.19
4.18
4.16
3.91
3.80
3.64
3.64
2.71
2.70
2.12
2.10
2.08
2.07
2.05
0.94
0.93
0.91
0.86
0.84
0.83
0.82
0.78
0.76
0.74
1.00
0.83
0.87
3.00
0.70
1.97
2.00
f1 (ppm)

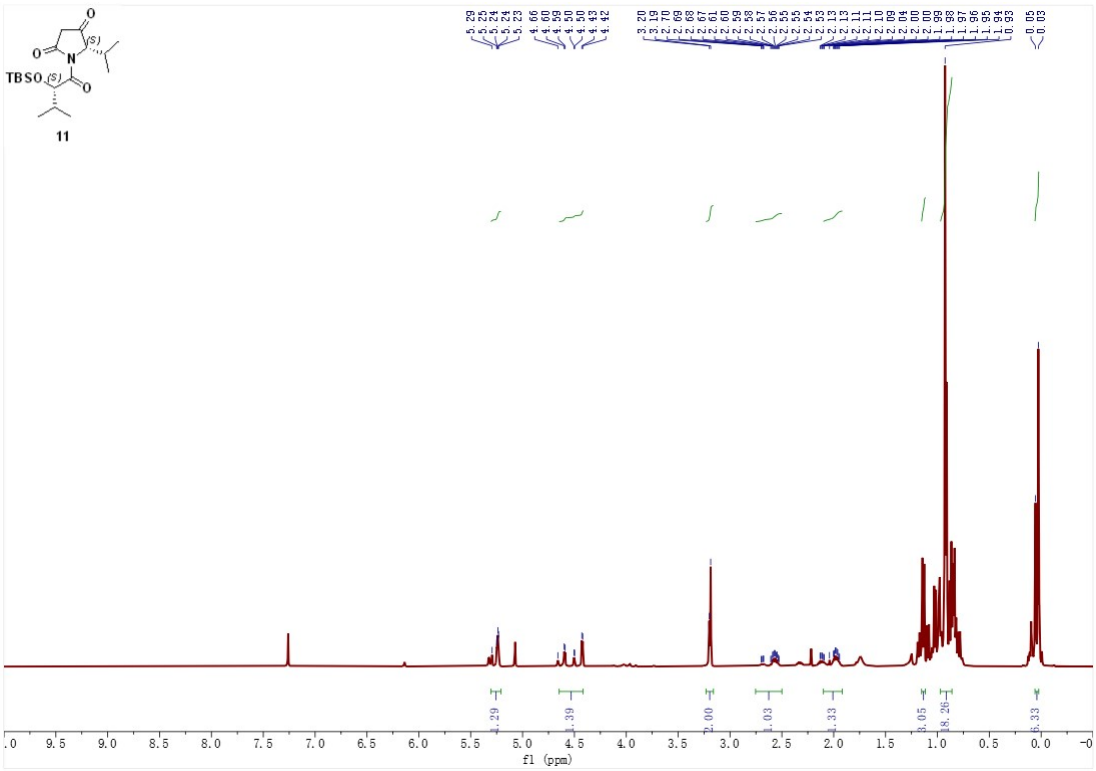

7
173.96
172.44
77.46
77.14
76.82
76.15
56.72
52.02
31.60
30.99
19.05
18.96
17.72
15.59
f1 (ppm)

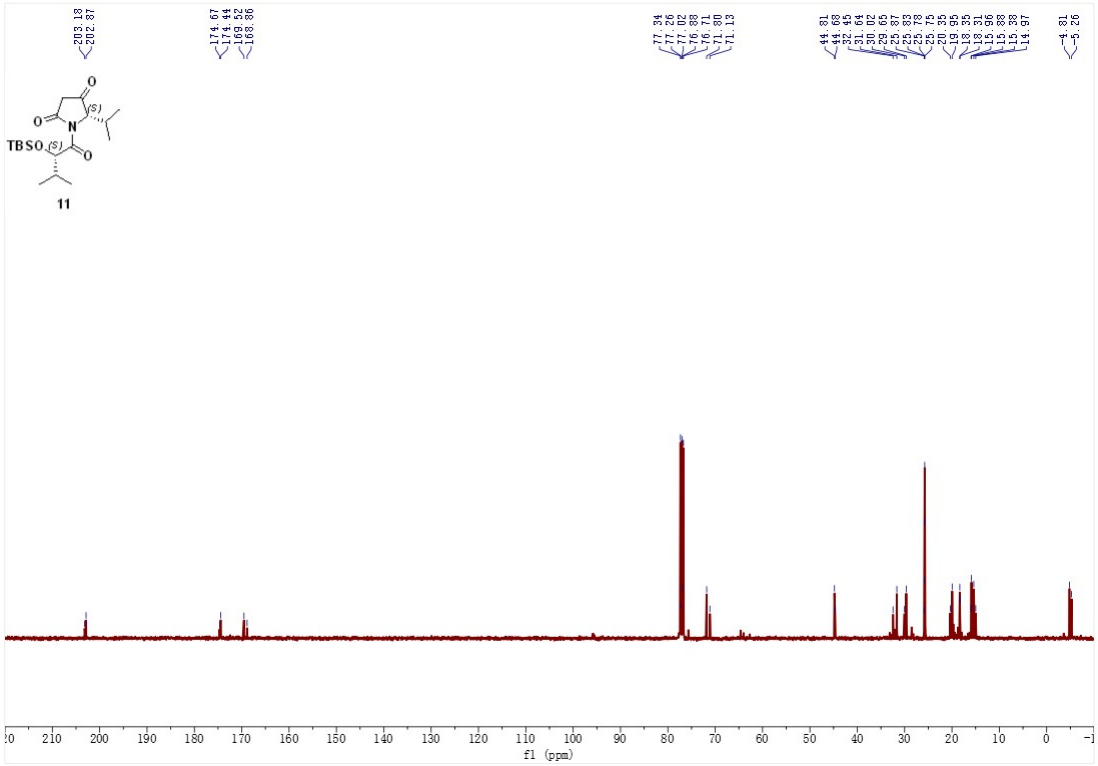

OTBS
(S)
(S)
8
7.26
7.01
6.99
4.53
4.52
4.51
4.50
4.49
3.95
3.94
3.93
3.89
3.88
0.95
0.94
0.92
0.90
0.89
0.88
0.87
0.86
0.85
0.06
0.05
0.93
0.98
0.99
3.00
2.03
9.25
11.93
6.18
f1 (ppm)

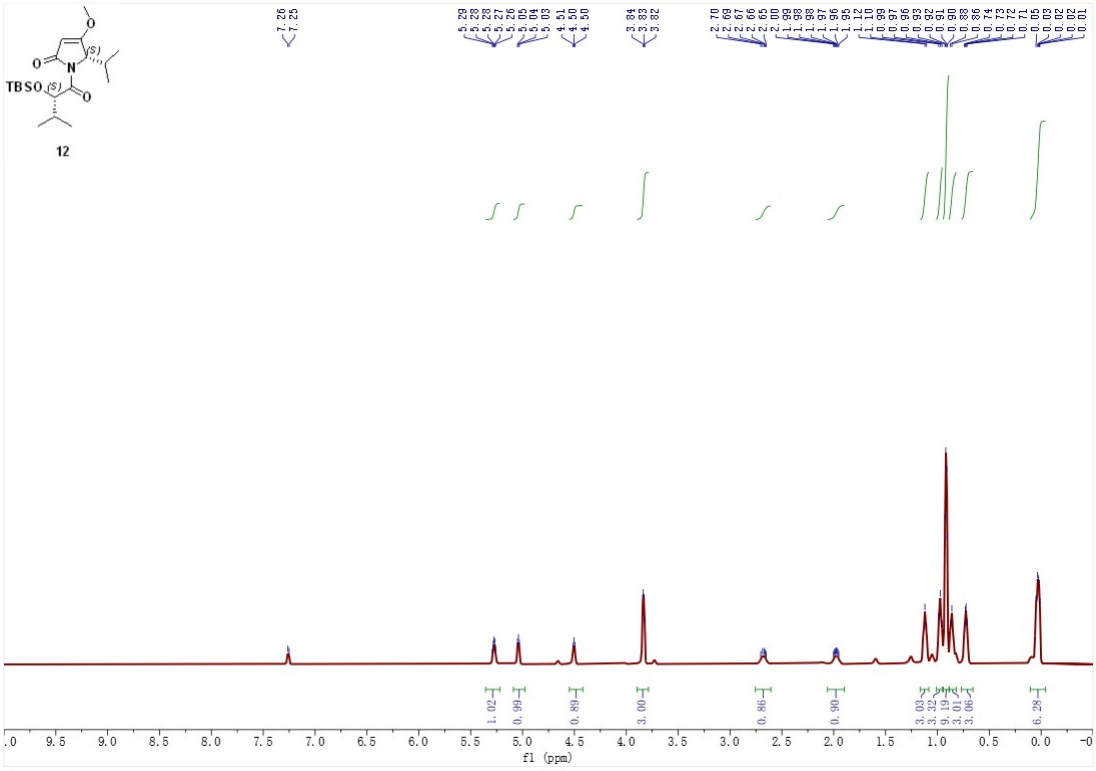

OTBS
(S)
(S)
8
173.04
171.86
77.69
77.37
77.05
76.73
56.46
51.87
32.67
31.19
25.73
19.31
19.03
17.96
17.66
16.24
-5.00
-5.26
f1 (ppm)

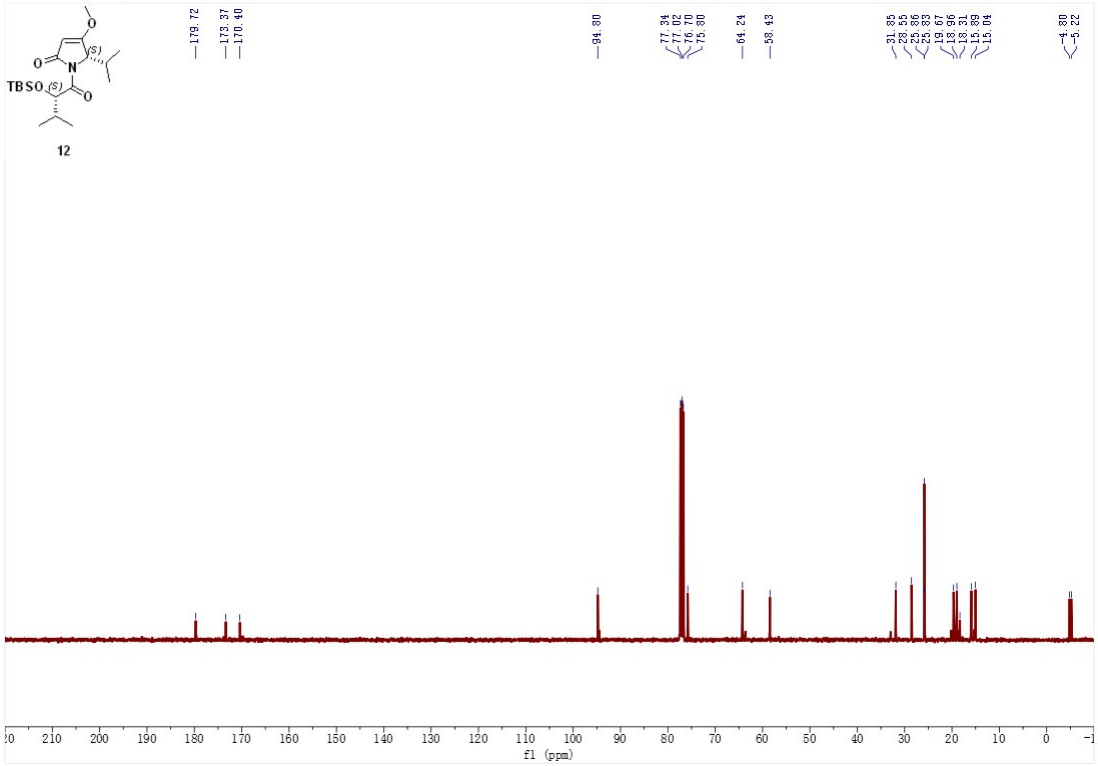

9
f1 (ppm)

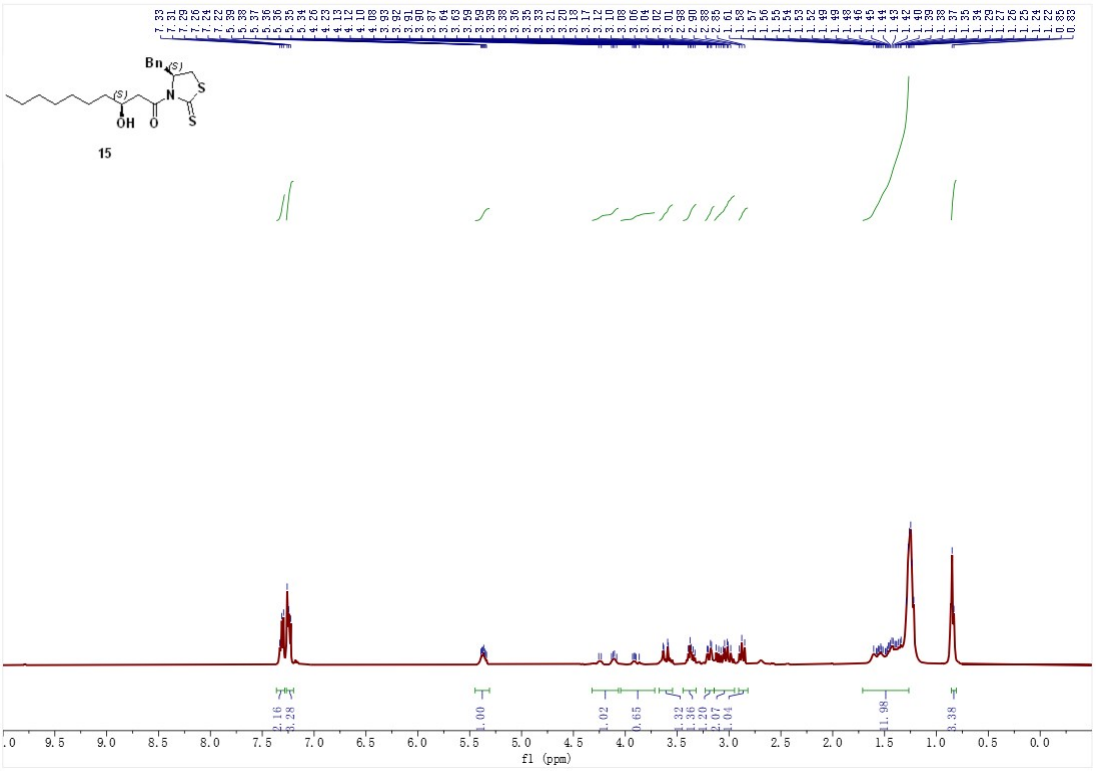

9
f1 (ppm)

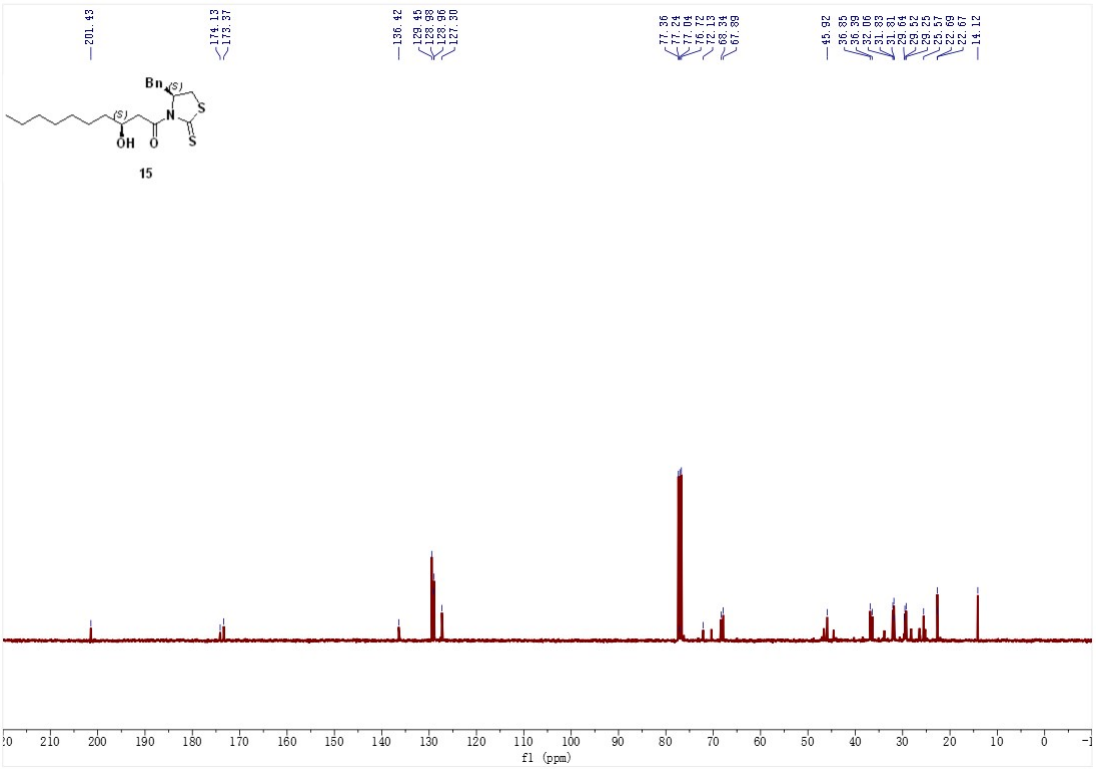

TBSO
11
f1 (ppm)


TBSO
11
f1 (ppm)


TBSO
12
f1 (ppm)


TBSO
12
f1 (ppm)


Bn
(S)
(S)
OH
O
N
S
S
15
f1 (ppm)


201.43
174.13
173.37
136.42
129.45
128.98
128.86
127.30
77.36
77.24
77.04
76.72
72.13
68.34
67.98
45.92
36.85
36.39
32.06
31.83
31.81
29.84
29.52
29.25
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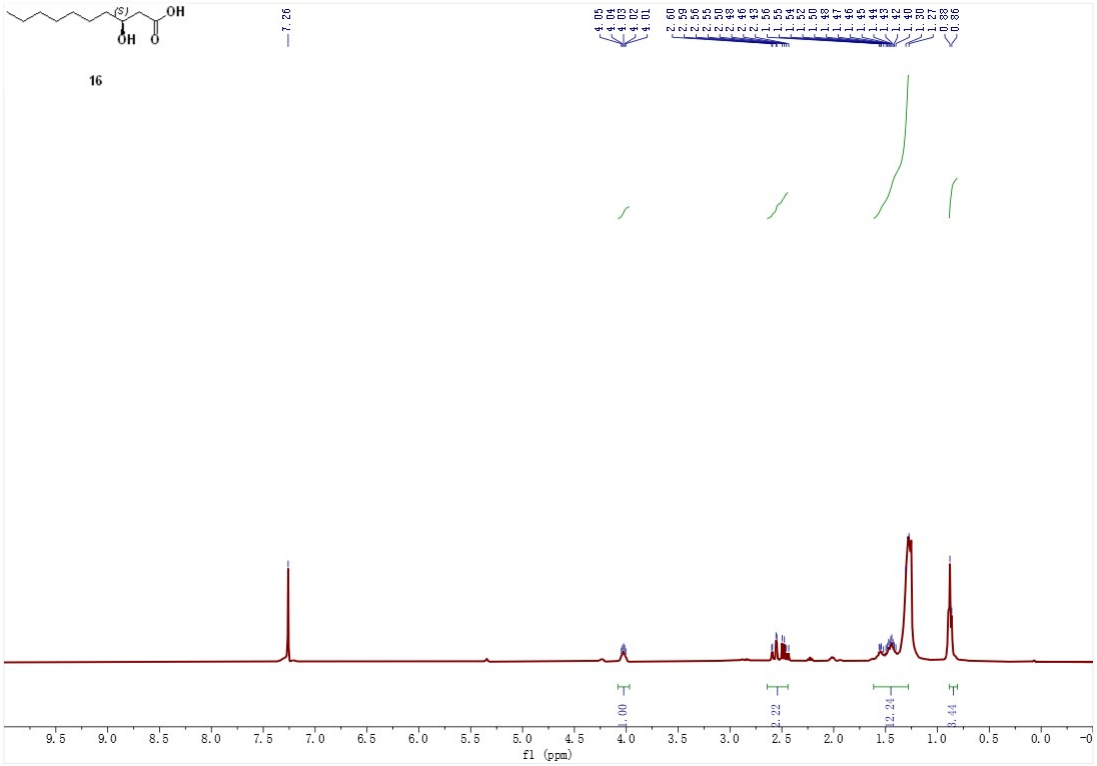
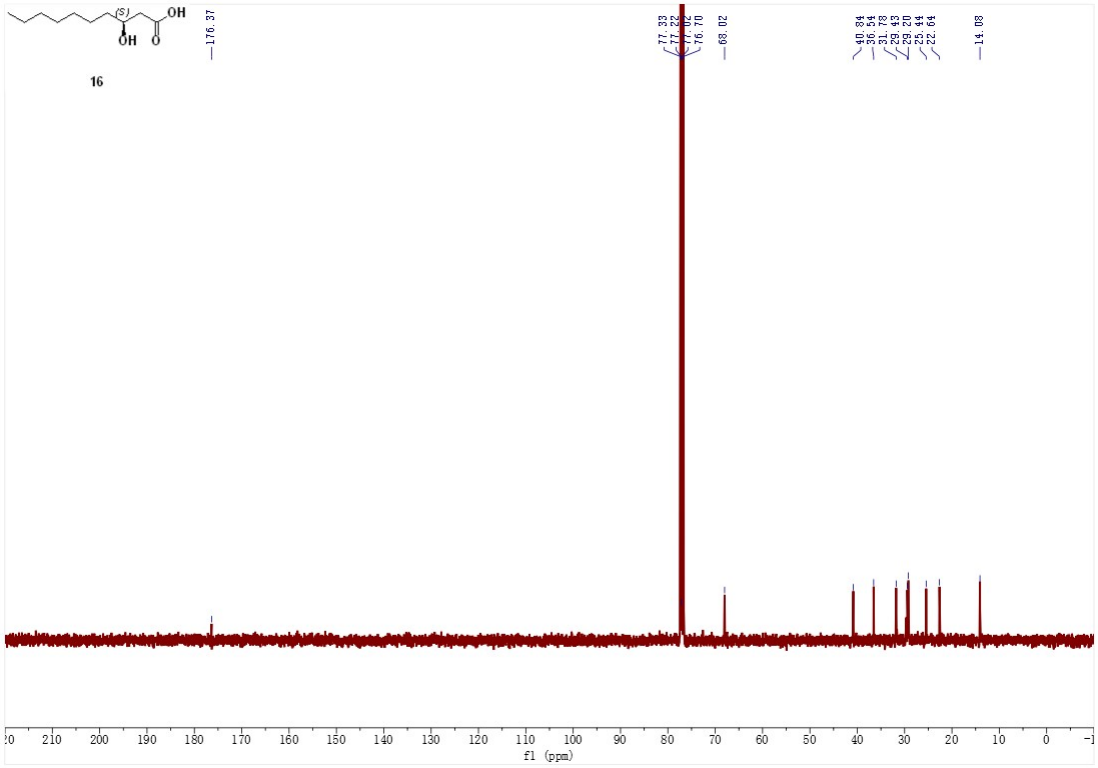
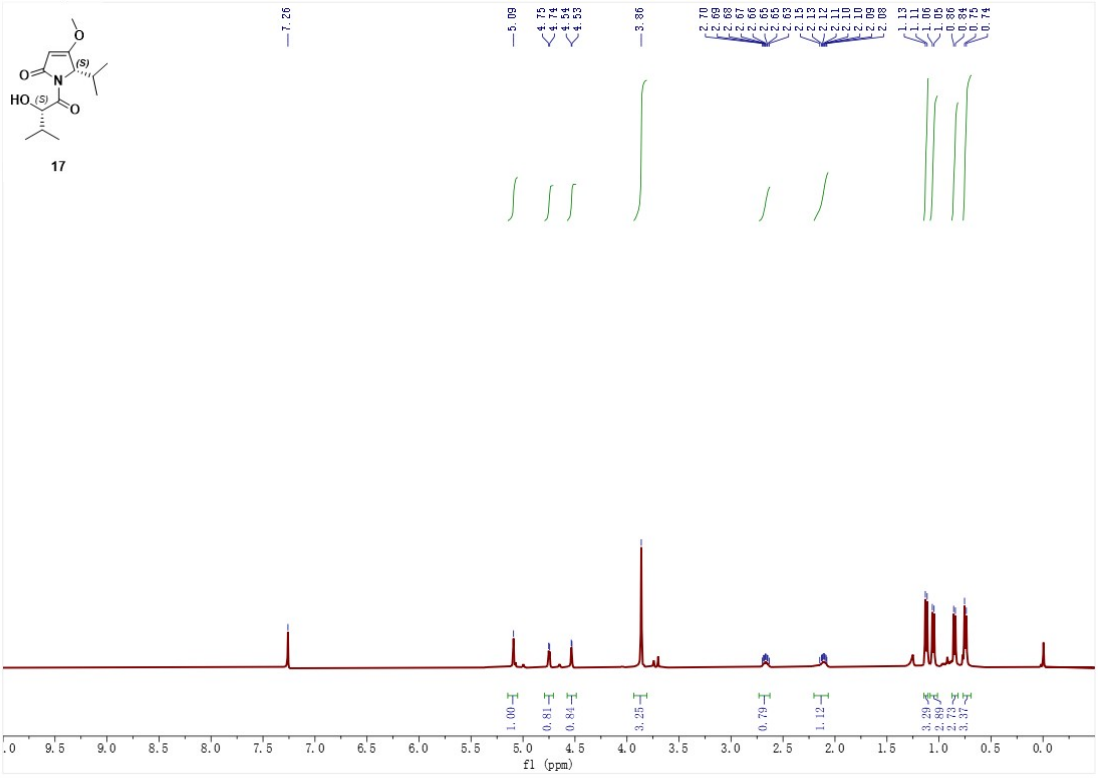
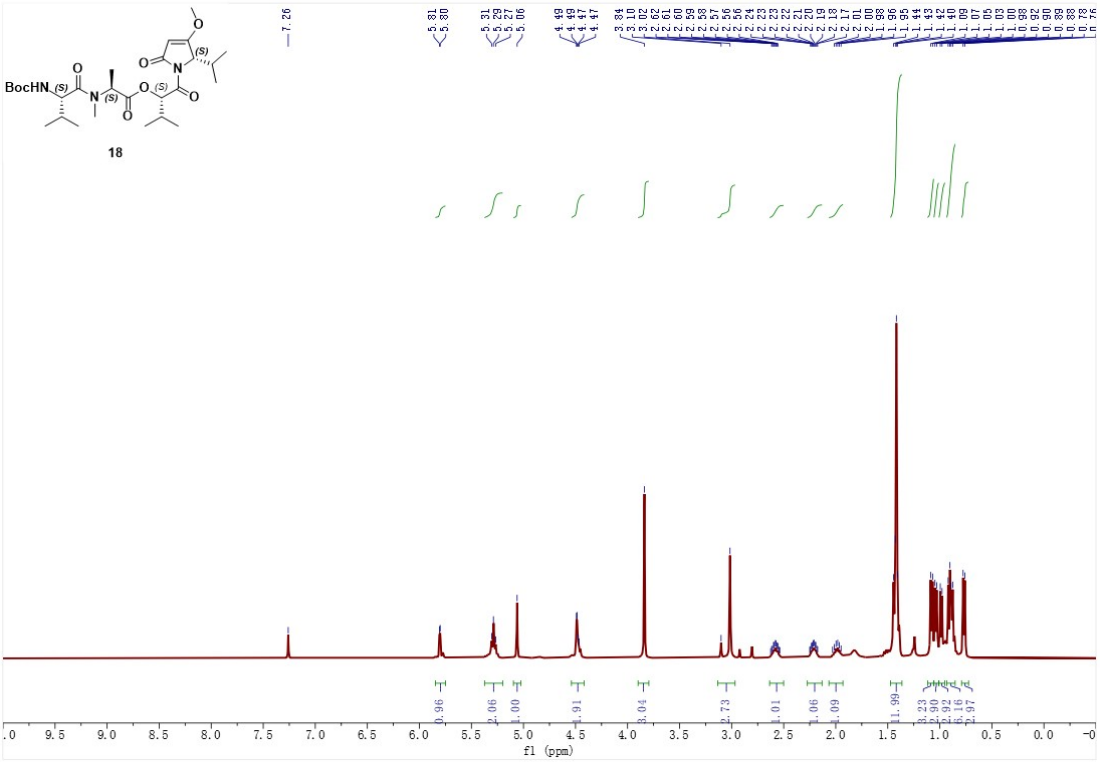
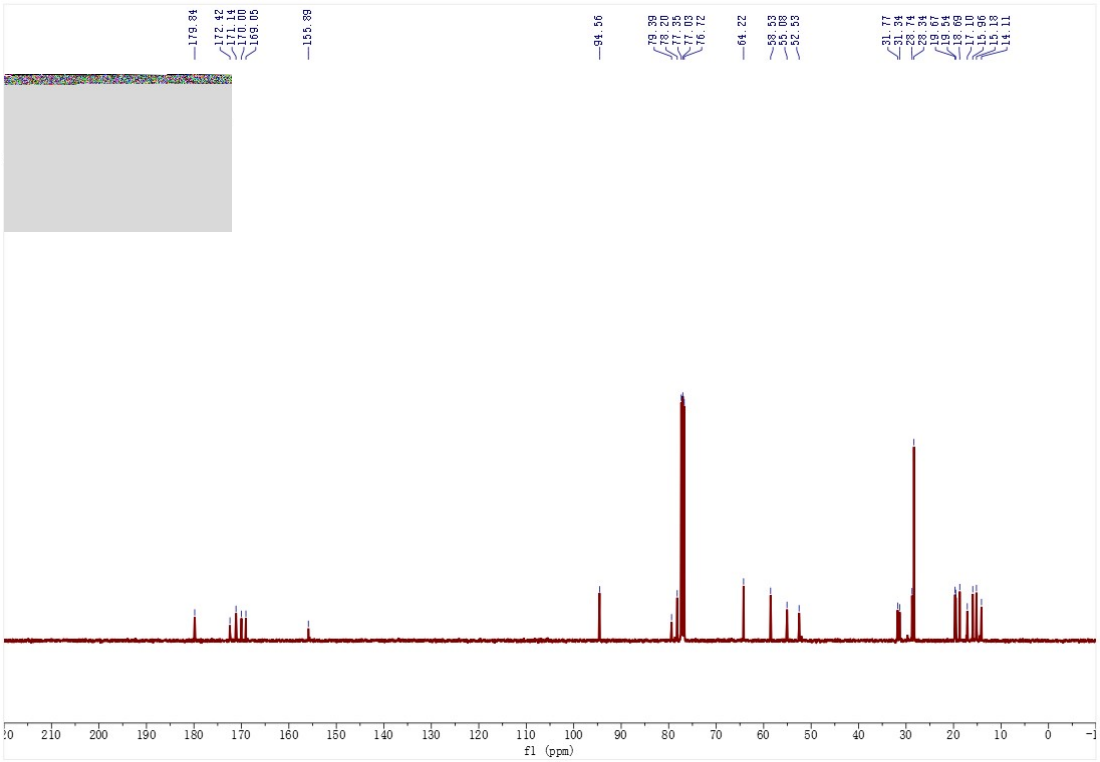
14.12
Bn
(S)
(S)
OH
O
N
S
S
15
f1 (ppm)

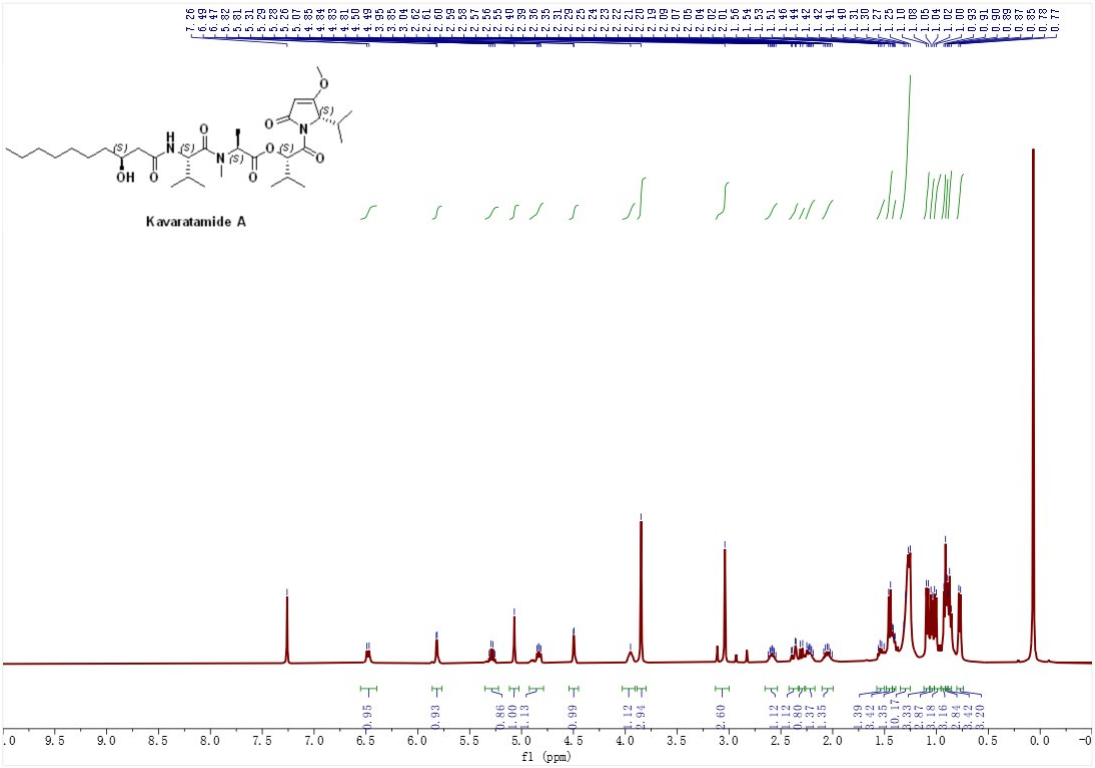

16
7.26
4.05
4.04
4.03
4.02
4.01
2.60
2.58
2.56
2.55
2.50
2.48
2.46
2.43
1.55
1.54
1.52
1.50
1.48
1.47
1.46
1.45
1.44
1.43
1.42
1.40
1.30
1.27
0.88
0.86
3.00
2.22
12.24
8.44
f1 (ppm)

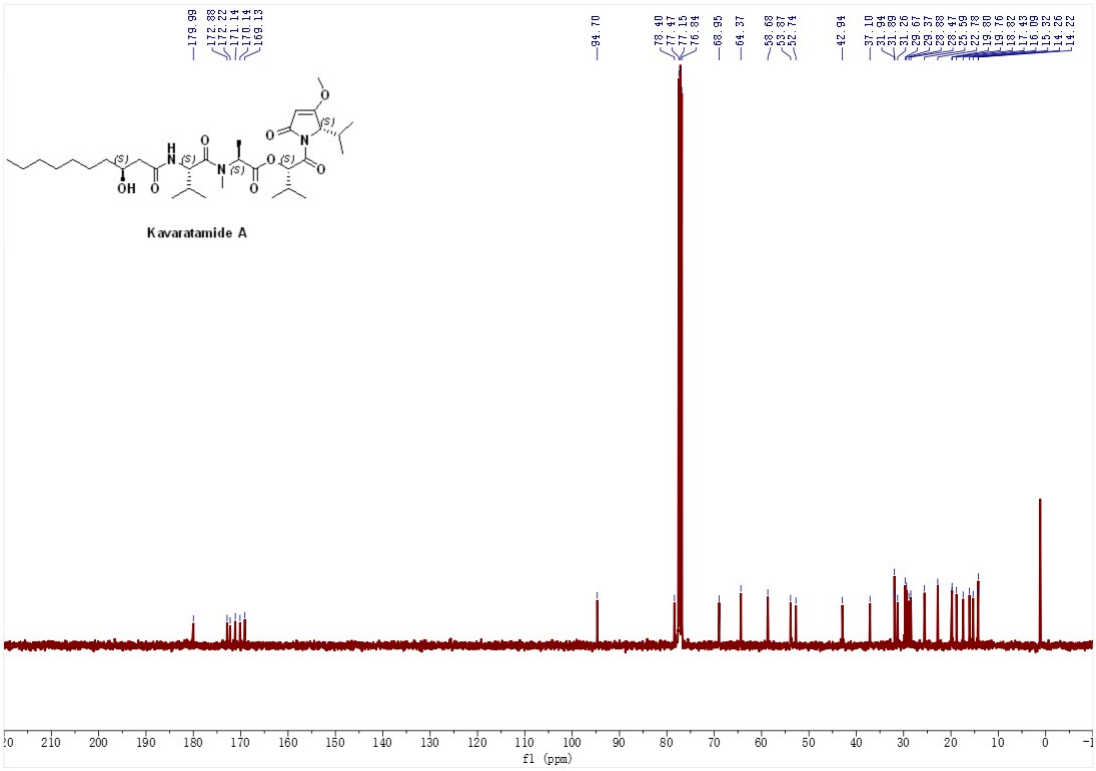

16
176.37
77.33
77.22
77.02
76.70
68.02
40.84
36.54
31.78
29.43
29.20
25.44
22.64
14.08
f1 (ppm)

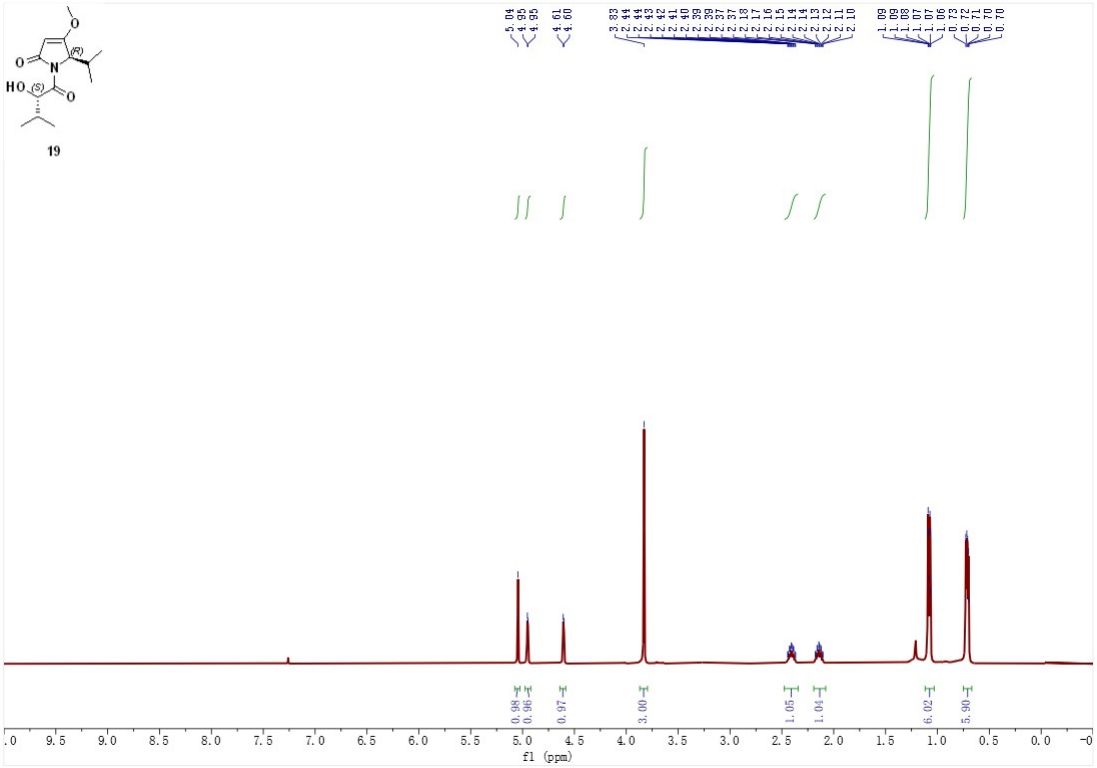

17
fl (ppm)

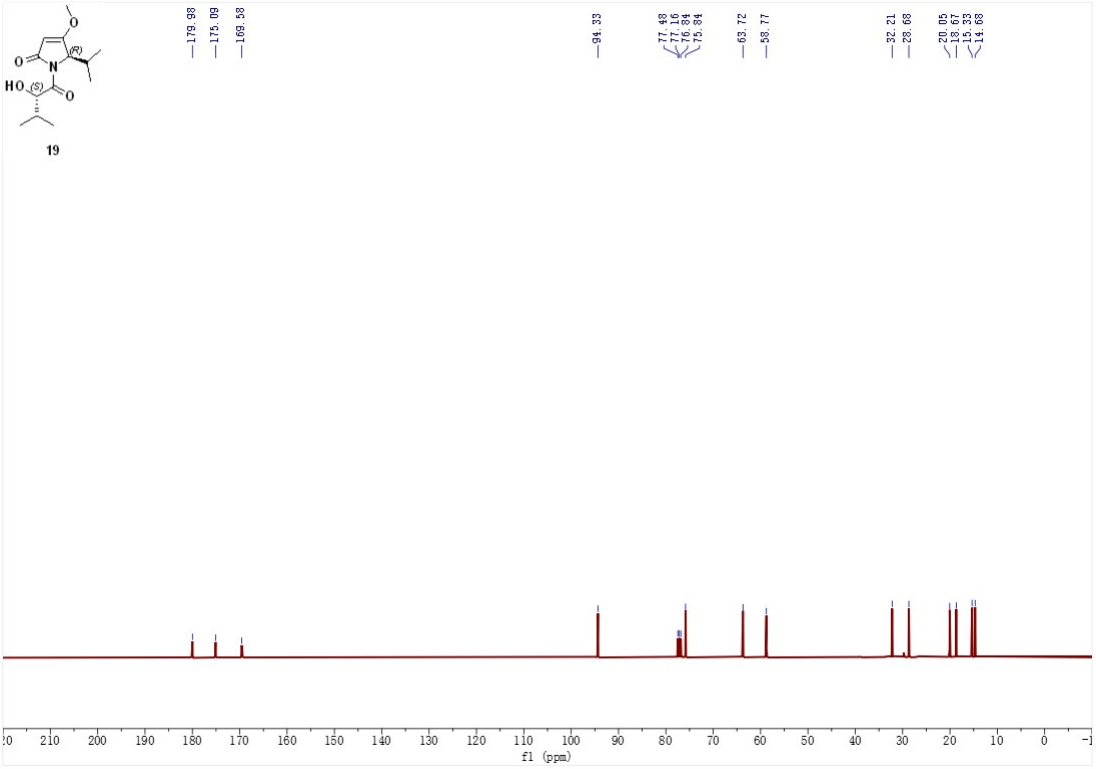

BocHN
18
fl (ppm)


179.84
172.42
171.14
170.00
169.05
155.89
94.56
79.39
78.20
77.35
77.03
76.72
64.22
58.53
55.09
52.53
31.77
31.34
28.74
28.34
19.67
19.54
18.69
17.10
15.66
15.18
14.11
f1 (ppm)


Kavaratamide A
f1 (ppm)


Kavaratamide A
f1 (ppm)


19
f1 (ppm)


19
179.98
175.09
169.58
94.33
77.48
77.16
76.84
75.84
63.72
58.77
32.21
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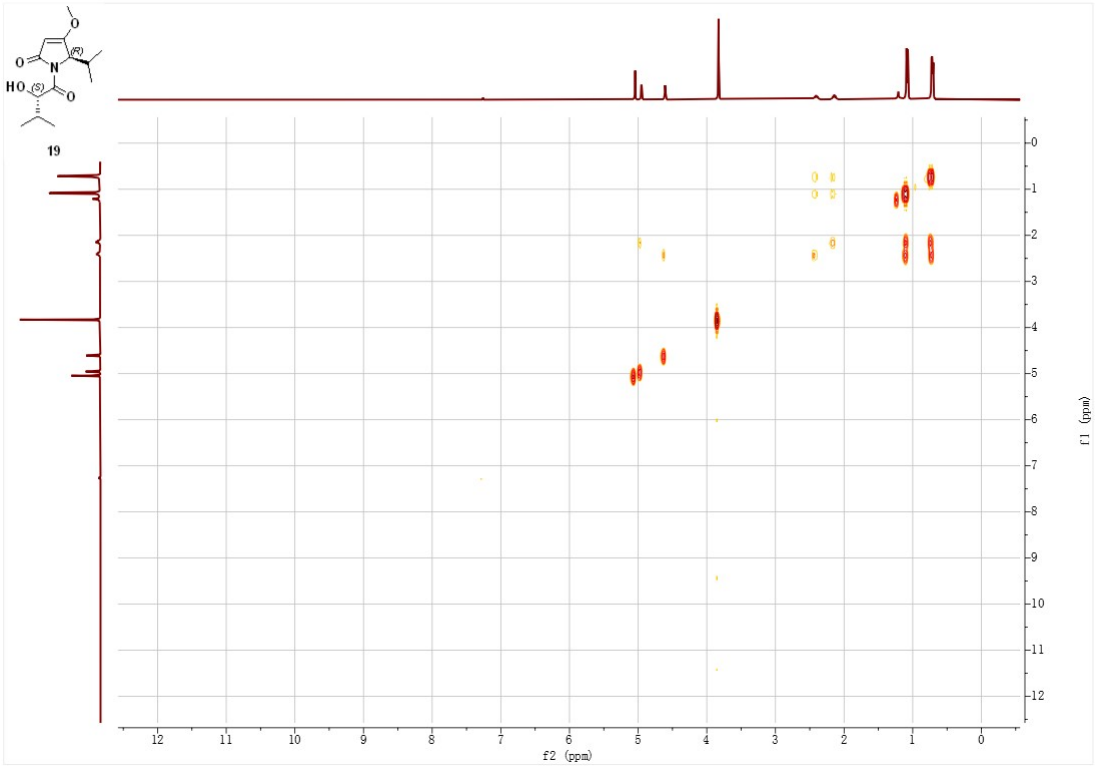
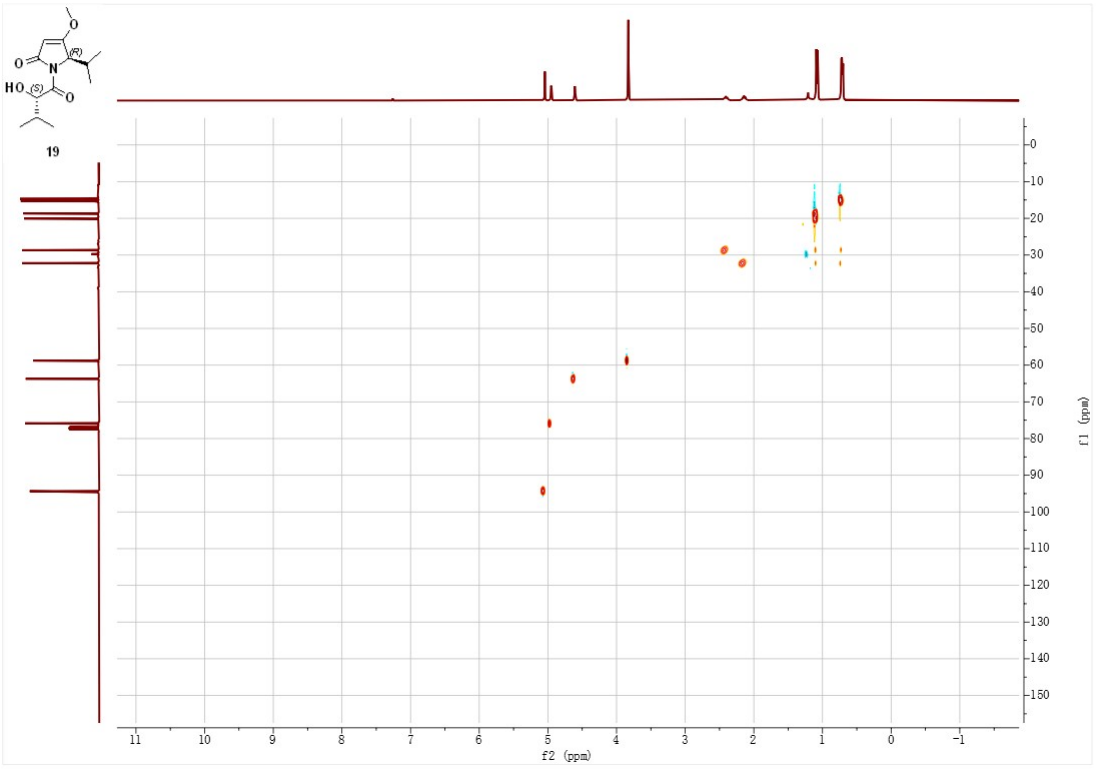
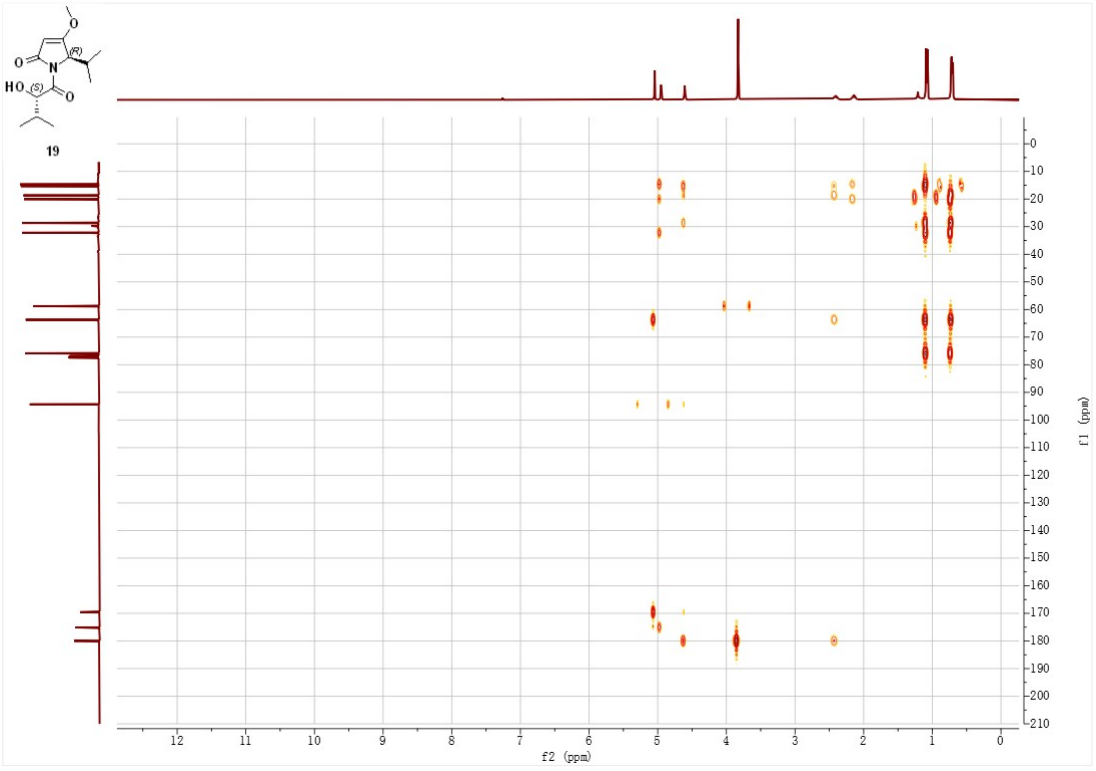
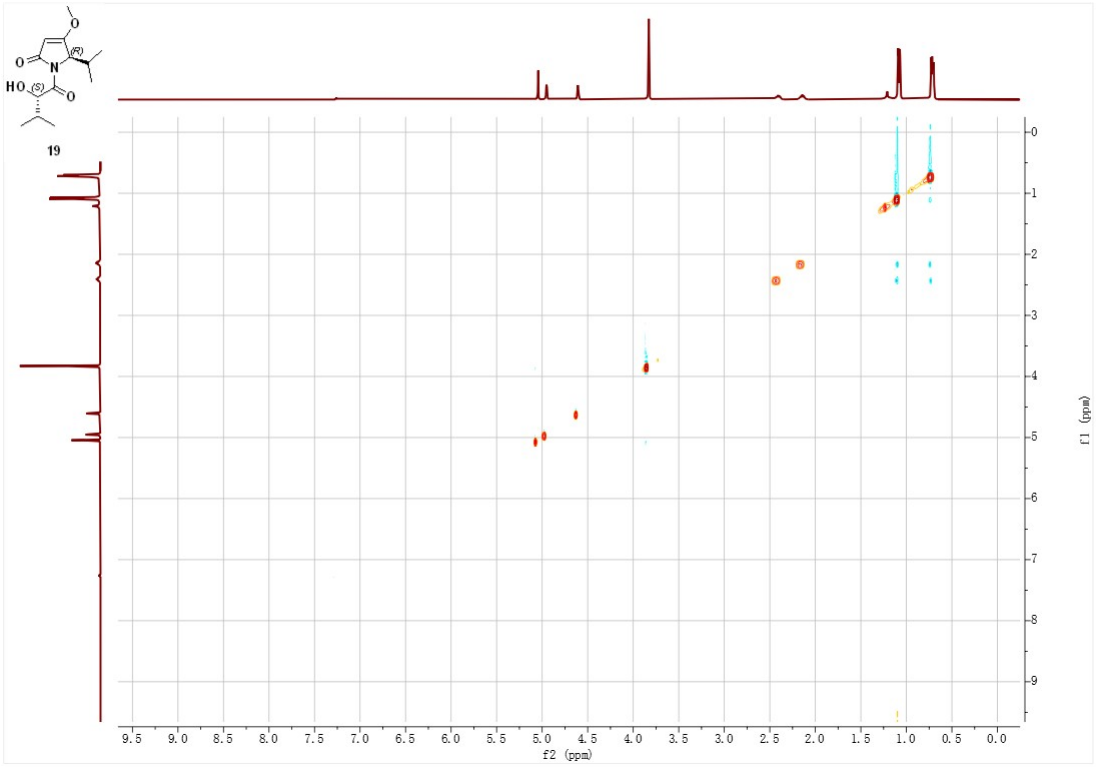
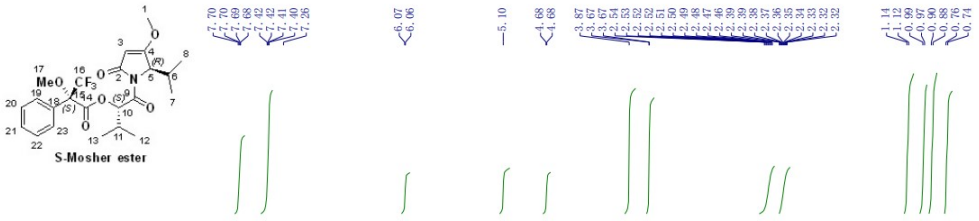
20.05
18.67
15.33
14.68
f1 (ppm)

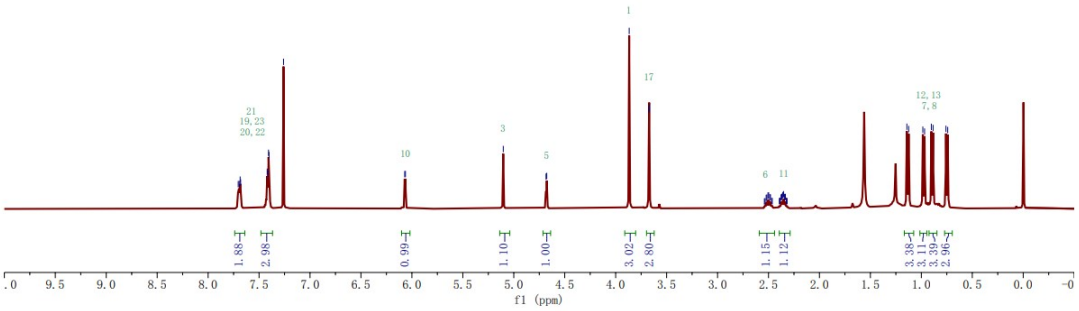

19
f2 (ppm)
f1 (ppm)

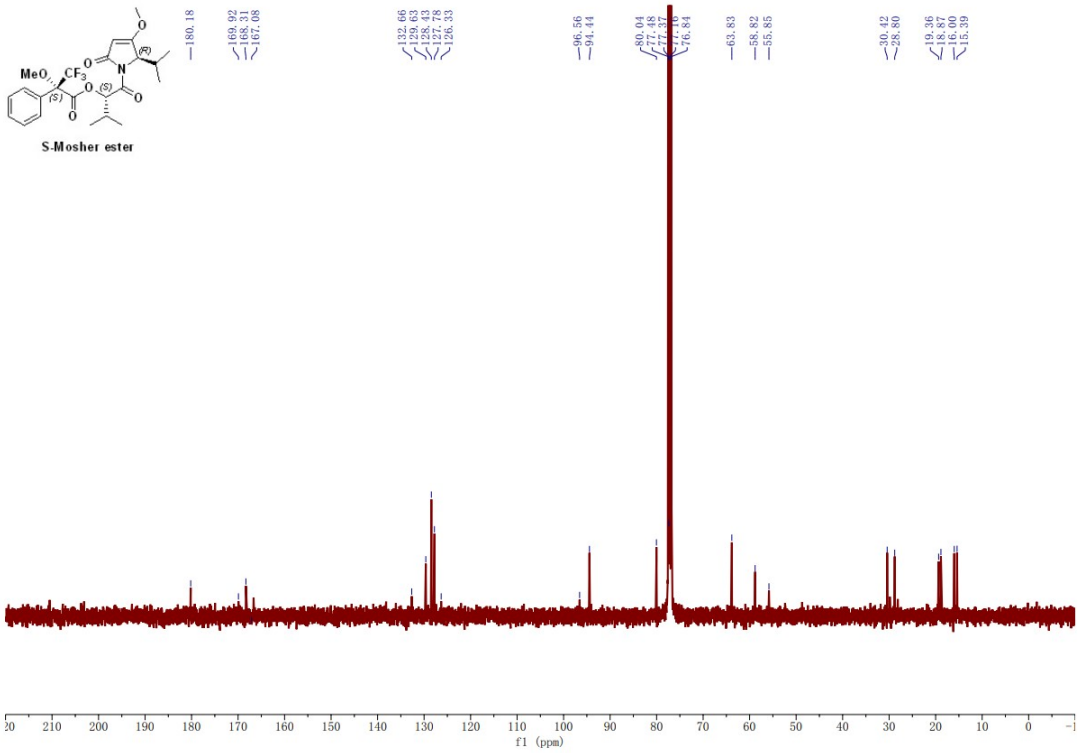

19
f2 (ppm)
f1 (ppm)


19
f2 (ppm)
f1 (ppm)

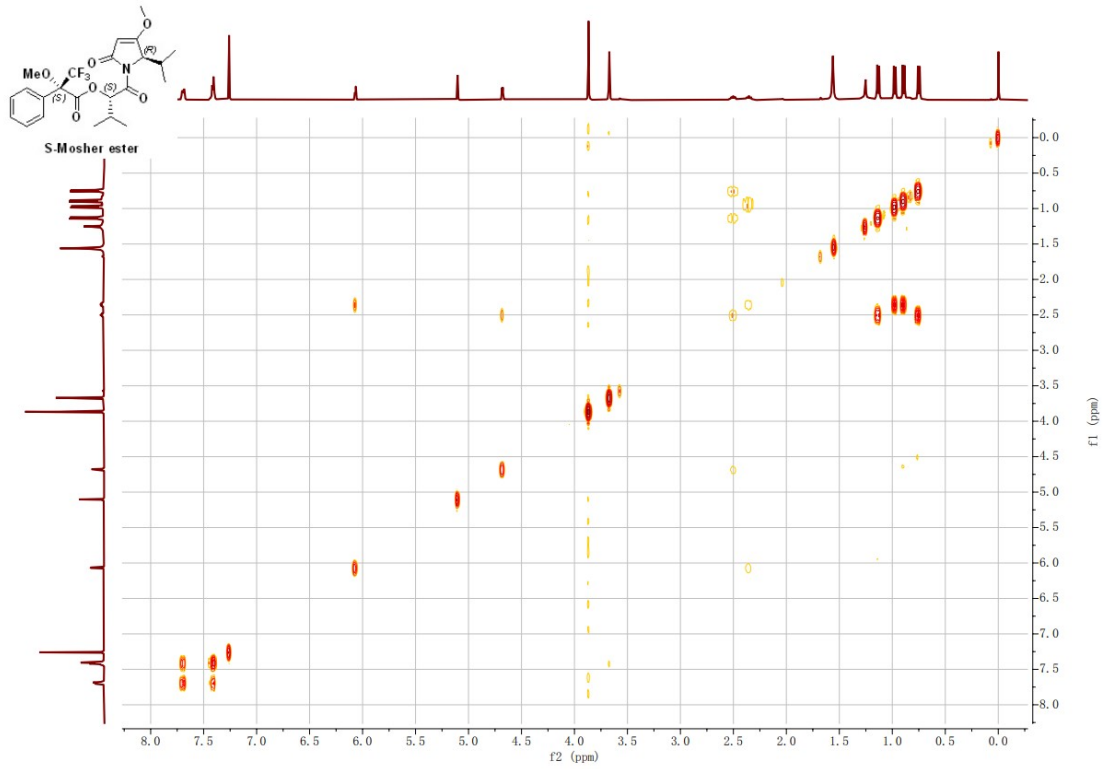

19
f2 (ppm)
f1 (ppm)


S-Mosher ester

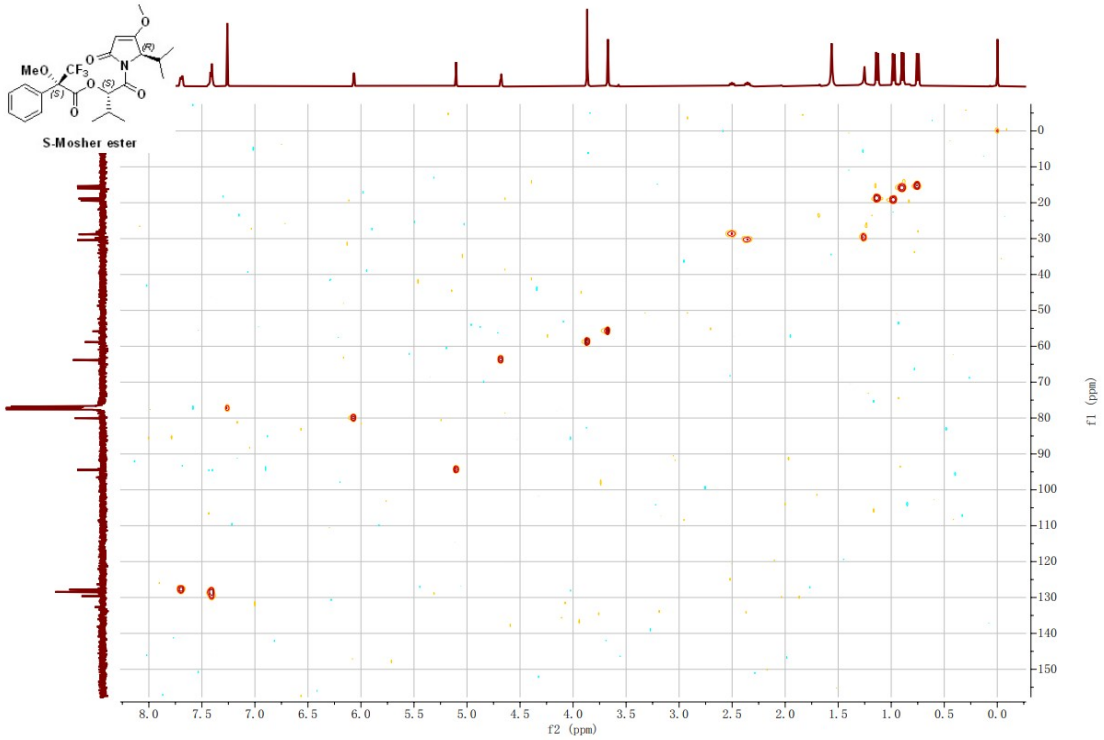

f1 (ppm)



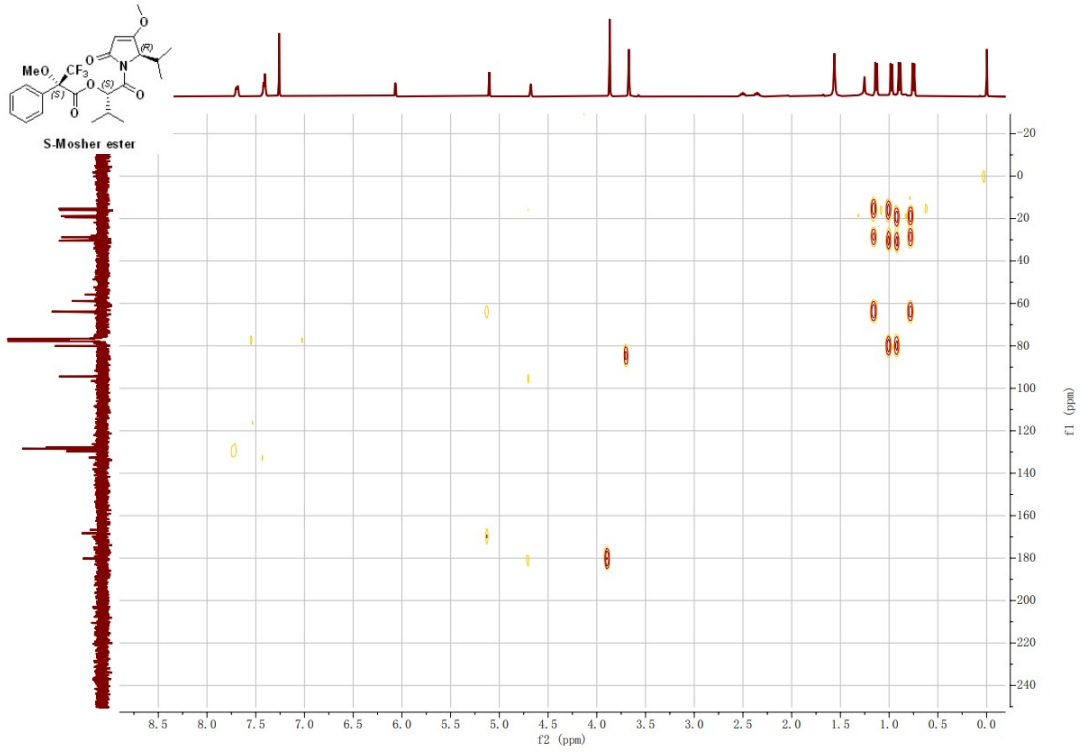
^{1}H-^{1}H COSY of *S*-Mosher ester

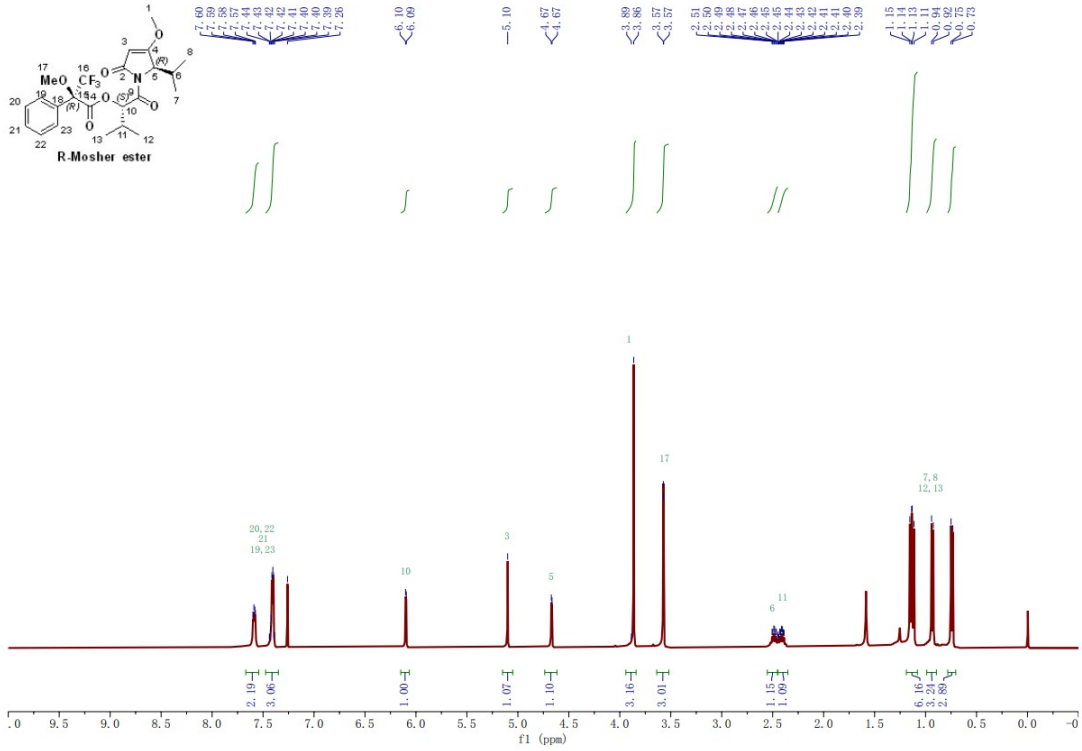


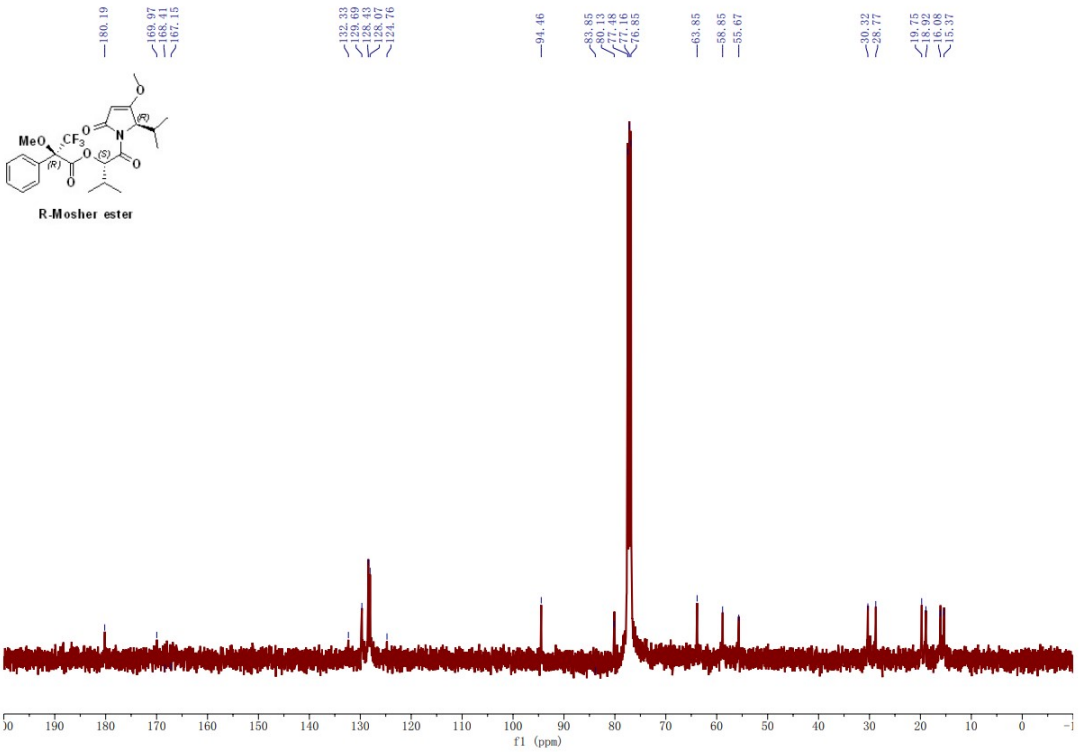
HSQC of *S*-Mosher ester



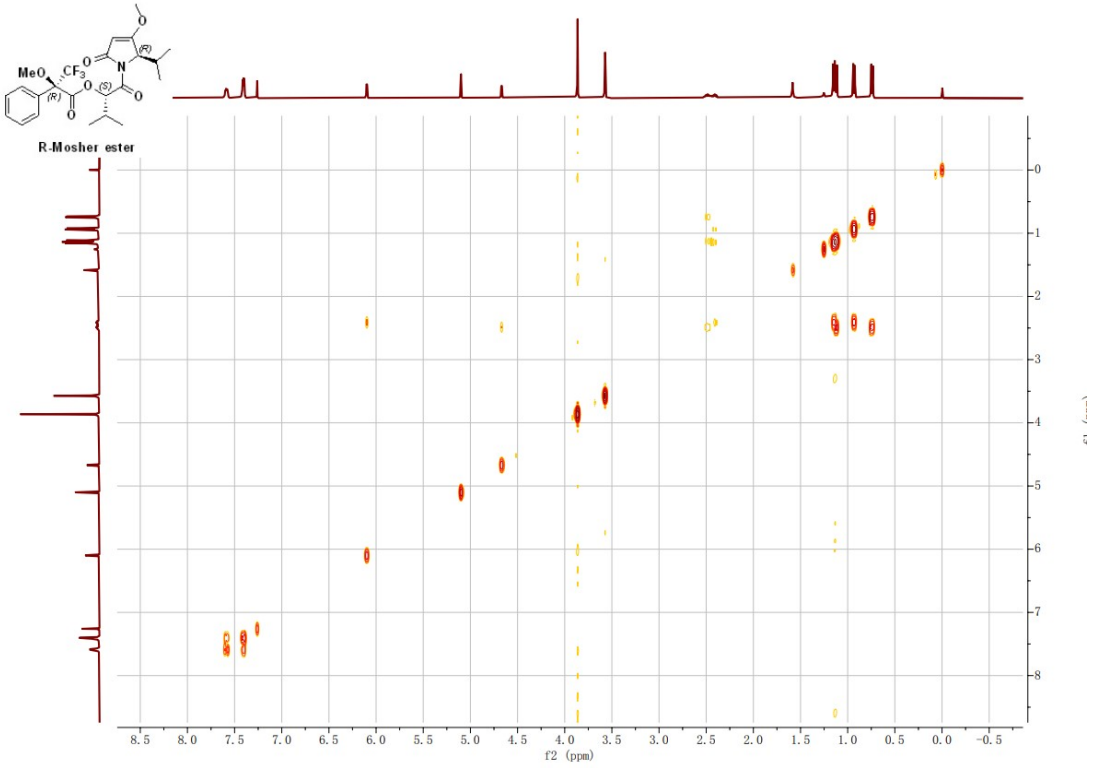
HMBC of *S*-Mosher ester



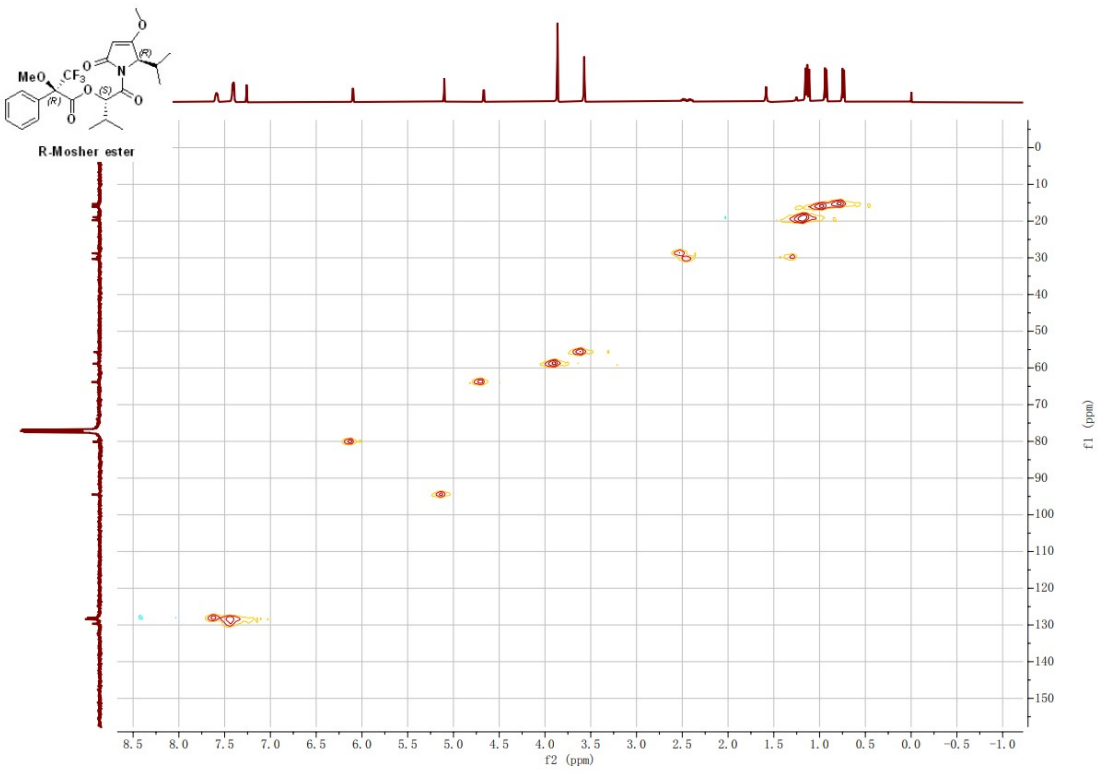

R-Mosher ester
f1 (ppm)


R-Mosher ester
f1 (ppm)

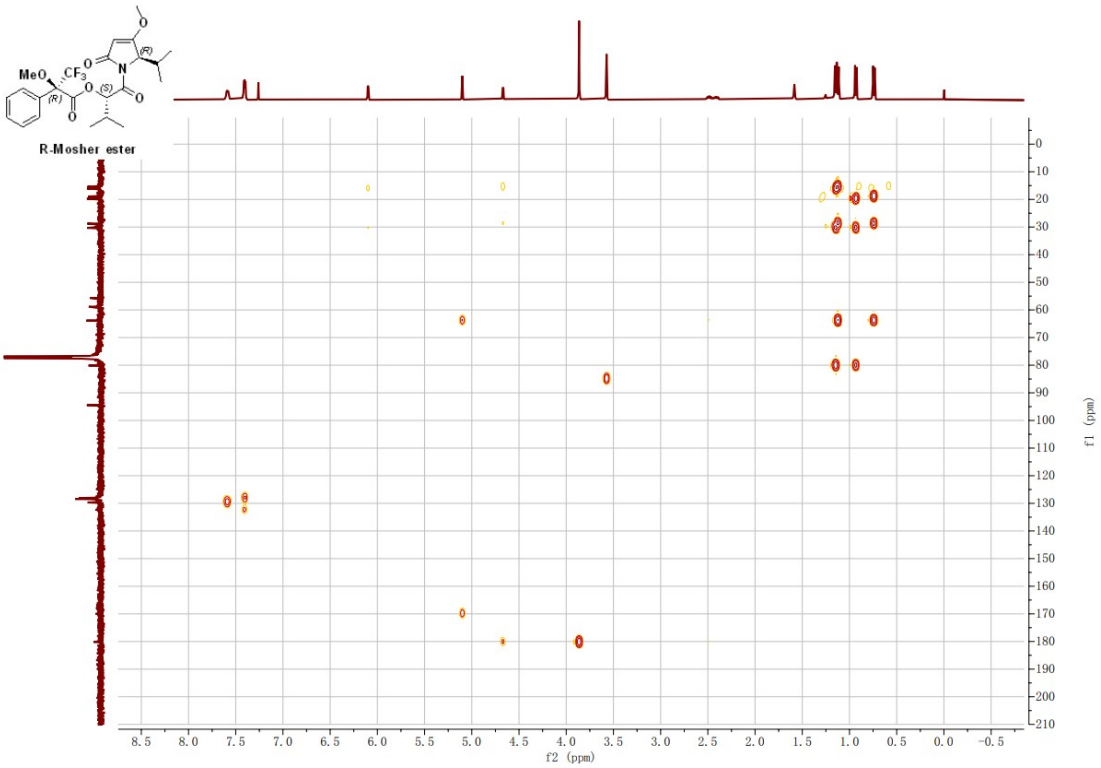
^{1}H-^{1}H COSY of *R*-Mosher ester

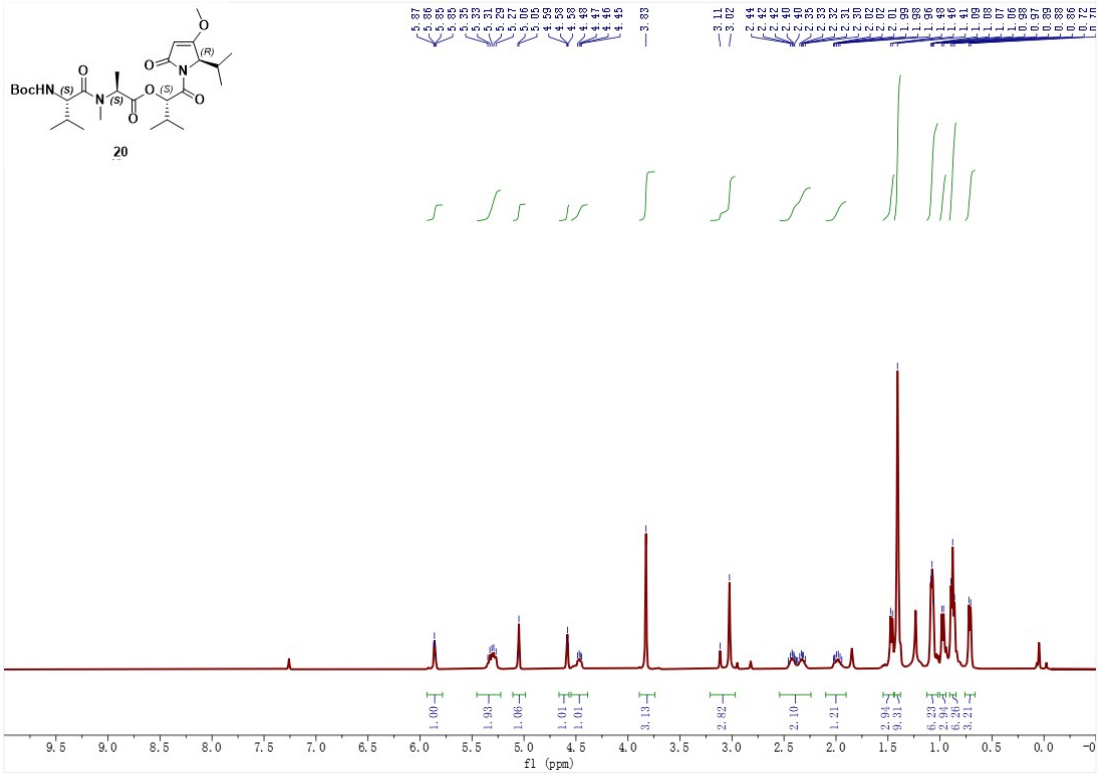


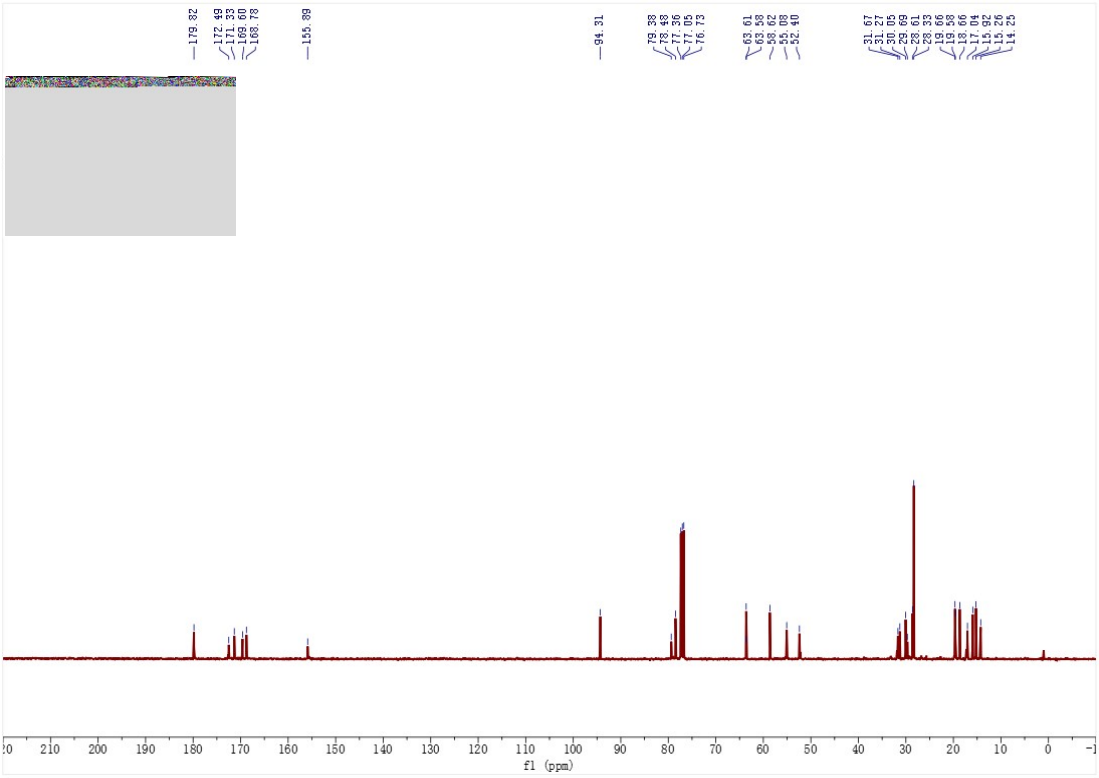
HSQC of *R*-Mosher ester



HMBC of *R*-Mosher ester






179.82
172.49
171.33
169.60
168.78
155.89
94.31
79.38
78.48
77.36
77.05
76.73
63.61
63.58
63.42
55.08
52.40
31.67
31.27
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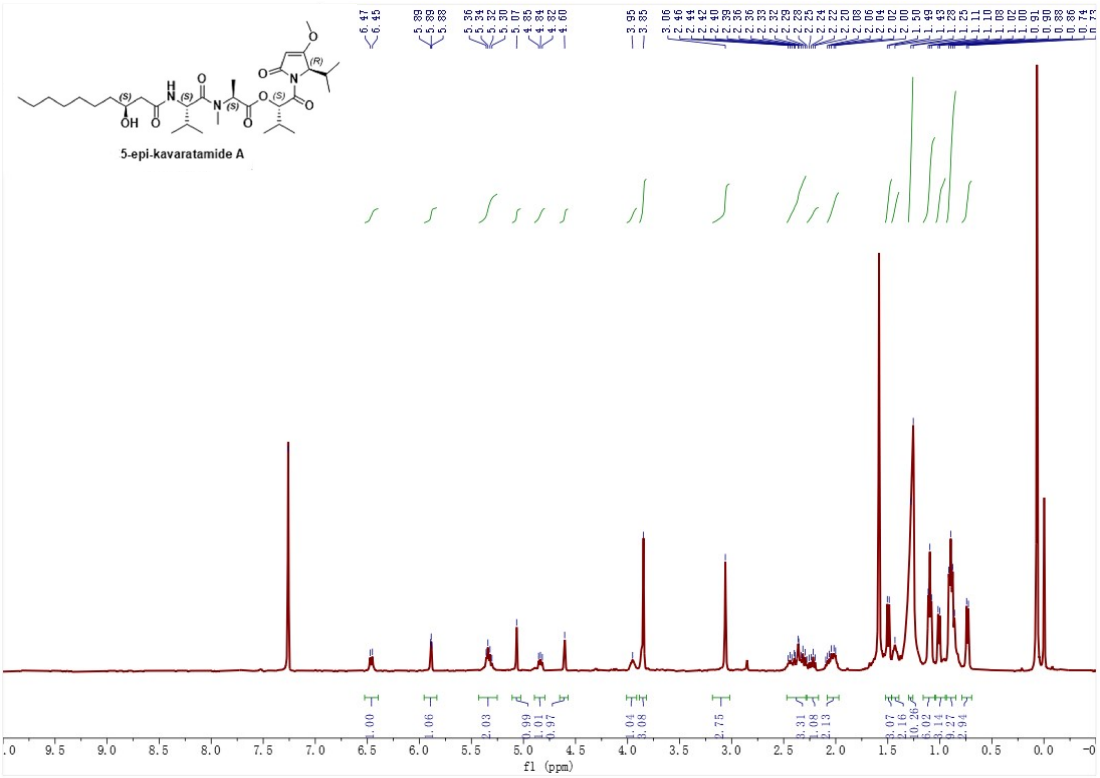
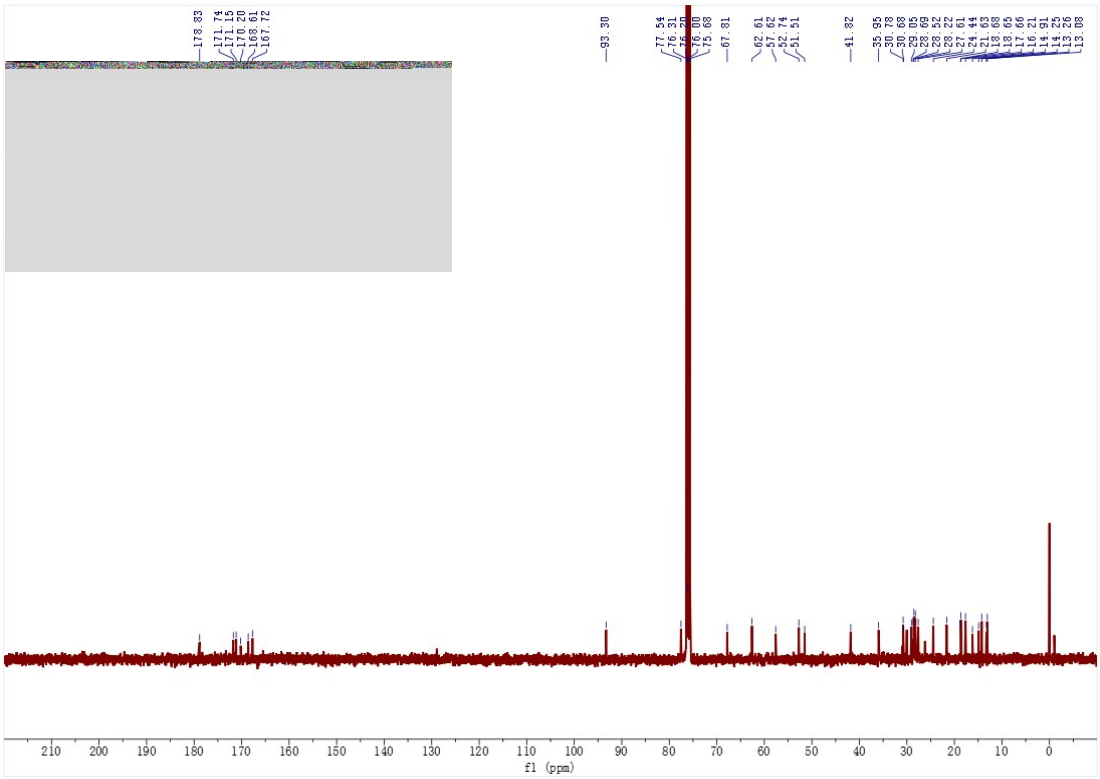
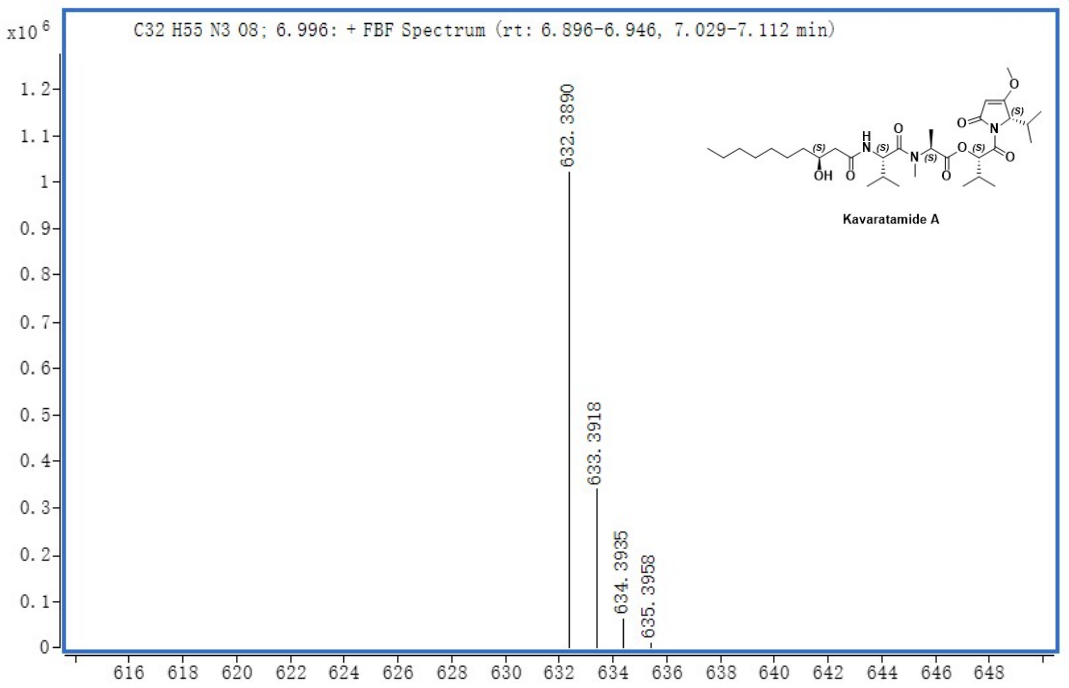
28.06
19.58
18.66
17.04
15.92
15.26
14.25
f1 (ppm)


5-epi-kavaratamide A
f1 (ppm)


178.83
171.74
171.15
171.00
168.61
167.72
93.30
77.54
76.31
76.20
76.00
75.68
67.81
62.61
57.62
52.74
51.51
41.82
35.95
30.78
30.68
29.05
28.69
28.52
28.22
27.61
24.44
21.63
18.68
18.65
17.66
16.21
14.91
14.75
14.25
13.08
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


C32 H55 N3 O8; 6.996: + FBF Spectrum (rt: 6.896-6.946, 7.029-7.112 min)
x10 6
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
632.3890
633.3918
634.3935
635.3958
616 618 620 622 624 626 628 630 632 634 636 638 640 642 644 646 648
Kavaratamide A